DOCTOR OF MEDICINE

Near infrared spectroscopy in cerebrovascular disease

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Near Infrared Spectroscopy in Cerebrovascular Disease

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To all the patients who allowed me to monitor them during surgery

Summary

Surgery for symptomatic high grade stenosis of the carotid artery has been proven to be of benefit in stroke prevention in two major international studies, the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial. In order to perform the surgery safely one tries to minimize the potential for both embolic load and ischaemia on the brain and to achieve this meticulous surgical technique and judicious use of carotid shunts are employed. To assist the operating surgeon in the decision of when to insert a shunt one can either perform the surgery under locoregional anesthesia or use an intra – operative monitor.

We have studied the newly developed system of near – infrared spectroscopy and shown that it is capable of accurately measuring change in intracranial haemoglobin in a cadaveric model, but with the limitation that the changes seen are not quantified. We have shown that the frontal position is easier to use and more accurate than the temporal. In the cases studied no change in cerebral oxygenation occurred with an embolic load, but no patient with emboli had a clinically detectable neurological injury and so one presumes that the emboli were not significant. The level of cerebral desaturation which can be tolerated varies from individual subjects but is statistically different between those under locoregional anaesthesia who have and do not have neurological compromise at carotid cross clamping, but with a large overlap between the two groups limiting application to patients under general anaesthesia.

The recommendation of the author would be that near – infrared spectroscopy is a useful research tool but is not helpful in decision making during carotid surgery.

Chapter 1 The History of Carotid Surgery

1.i. Anatomy and Physiology

The human cerebral circulation receives its blood supply from the carotid arteries anteriorly and vertebral arteries posteriorly; on the right the common carotid and subclavian arteries arise from the division of the brachiocephalic trunk which in turn arises from the arch of the aorta, with the vertebral being the first branch of the subclavian. On the left the common carotid and subclavian are direct branches of the arch of the aorta, with the vertebral again being the first branch of the subclavian.

On both sides the common carotid divides into an external and internal branch, being easily distinguished from each other by the presence of extracranial branches on the external carotid. The site of this bifurcation is variable. The internal carotid passes through the carotid syphon to enter the middle cranial fossa from where it divides into the anterior and middle cerebral arteries.

The vertebral arteries on both sides pass posteriorly to enter the foramen transversarium of the seventh cervical vertebrae, they then travel upward through the foramina of subsequent cervical vertebrae until they enter the cranial cavity via the foramen magnum. The two then combine to form the single basilar artery. This travels forward giving multiple branches to supply the posterior cranial fossa before dividing into the posterior cerebral arteries. The posterior and anterior circulations are connected by the posterior communicating arteries, forming the Circle of Willis. From this multiple branches arise to provide all regions of the cerebral hemispheres with an adequate supply (see fig 1.1 and 1.2).

Fig 1.1. Anatomical diagram of the base of the brain

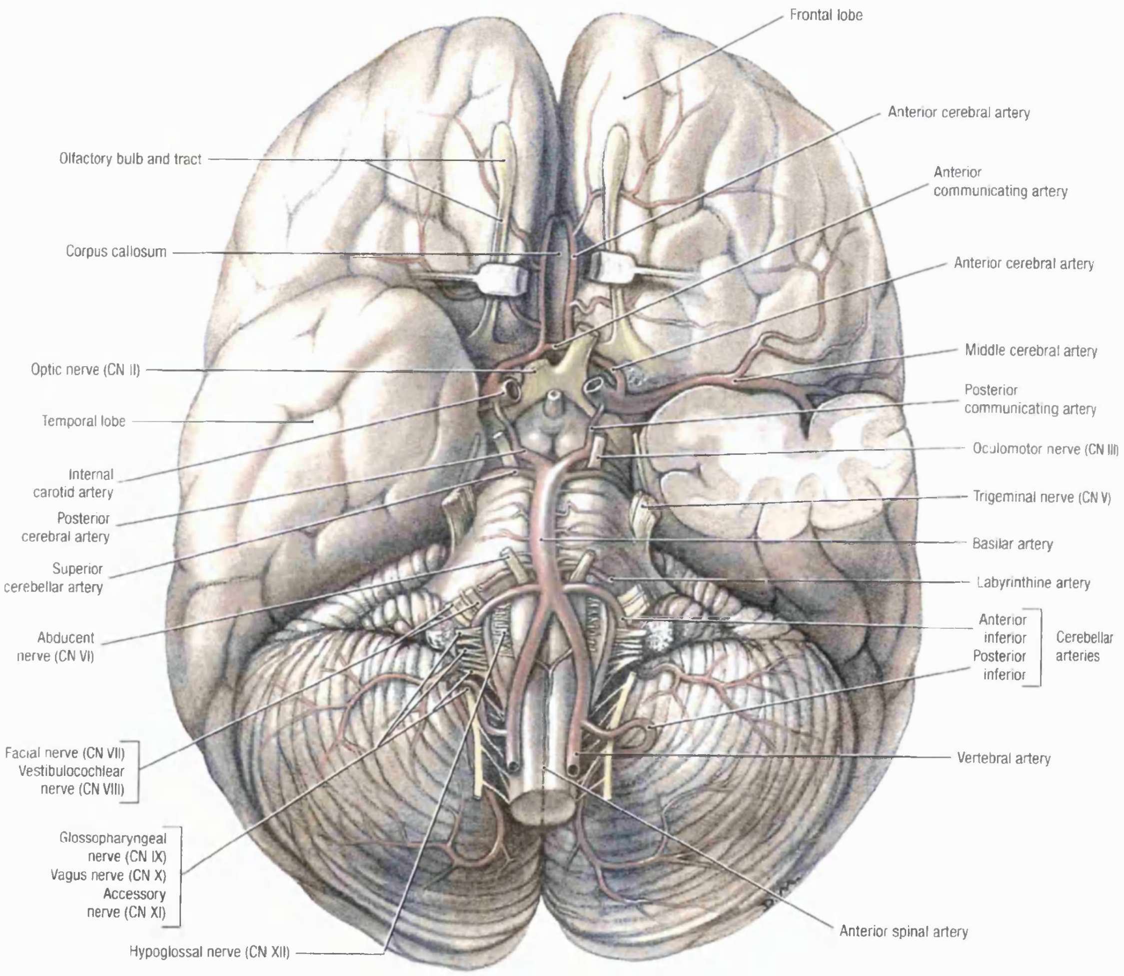
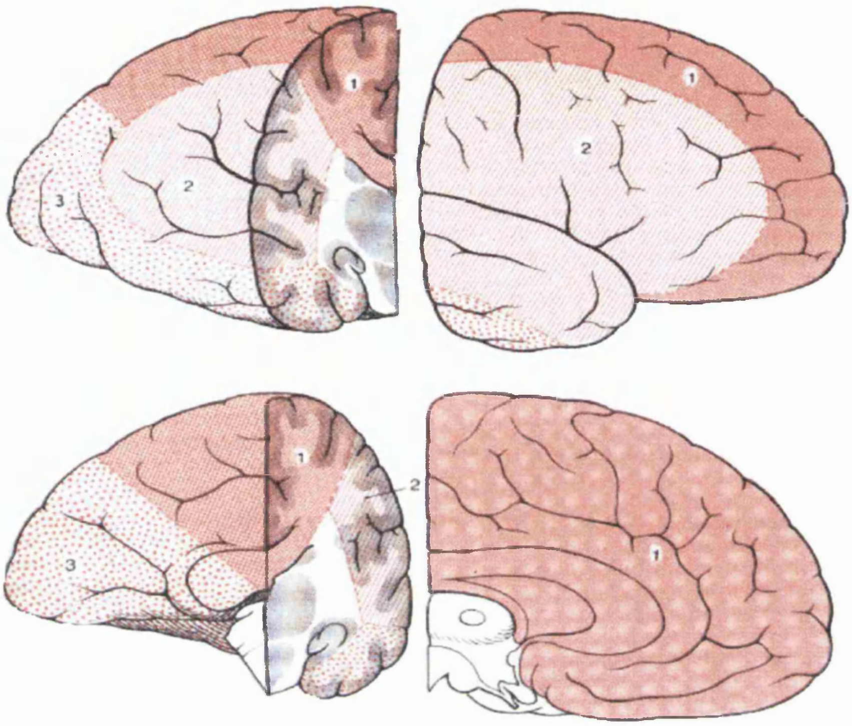


Fig 1.2. Regional blood supply of the brain



1. Anterior Cerebral Artery
2. Middle Cerebral Artery
3. Posterior Cerebral Artery

In most humans' the circulatory anastomosis is complete, allowing blood flow and supply to remain constant in situations of decreased flow through one or more vessels. Unfortunately this is not the case in all, and interruption of flow in one vessel can lead to cerebral hypoxia, progressing to ischaemia and irreversible cell death unless manoeuvres are undertaken to restore the status quo.

In addition to the anatomical design of the circulation, our bodies have a complex system of regulatory mechanisms which are designed to ensure that the flow of blood to the brain remains adequate at all times and preferentially at the expense of other organs. The carotid bifurcation has a rich plexus of nerves called the carotid sinus which arise from the glossopharyngeal nerve (IX cranial nerve), and which send information regarding both the pressure and chemical constitution of the blood. This enables the cardiorespiratory centre of the brainstem to make adjustments to heart and respiratory rate under circumstances such as hypoxia, hypercarbia, change in pH or hypovolaemia to maintain the brain's internal milieu.
As well as this extracranial control the brain's vasculature is designed so that the intracranial blood pressure is relatively constant through the normal physiological range of blood pressures(1), however this control fails at extremes of hyper - or hypo - tension (see fig 1.3). Pharmacological intervention, alcohol, extremes of temperature and sepsis all change the response of human vasculature either through direct or indirect action so that the below graphical representation of cerebral response does not apply in all situations, but is indicative of the preferential supply that the brain receives.

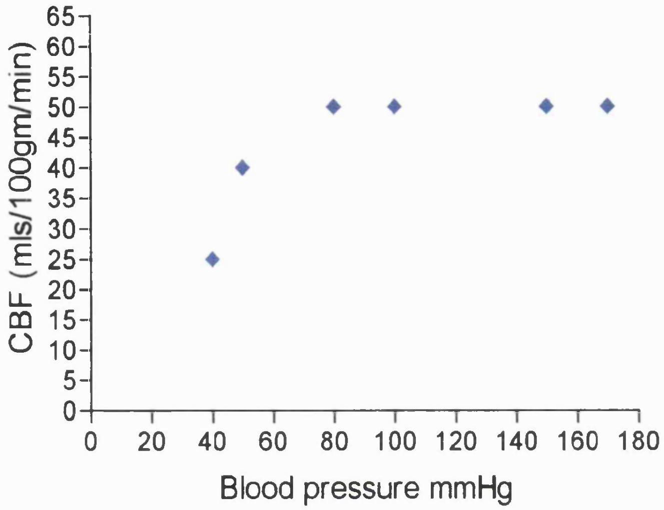


fig 1.3. Cerebral autoregulation with changes in blood pressure

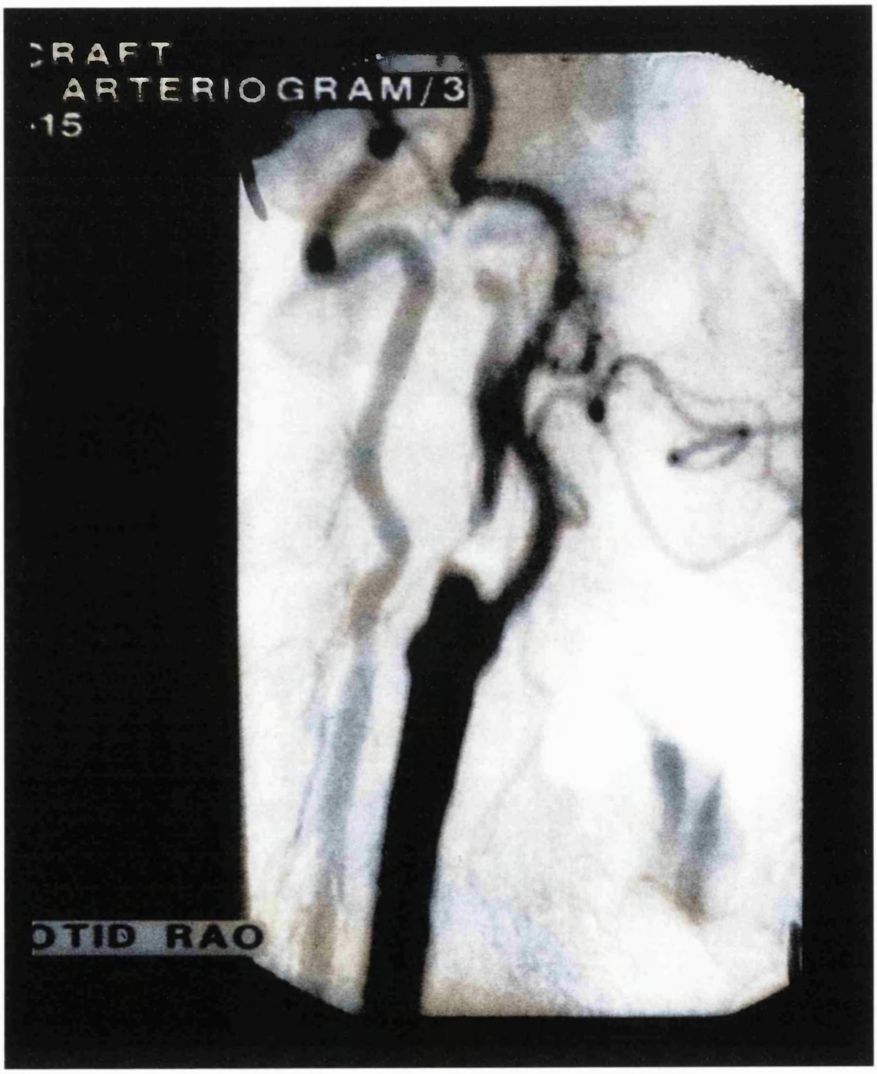
(modified from Guyton and Hall, Textbook of Medical Physiology, 9th edition, Saunders)

1.ii. History

It has been known since ancient times that pressure over a carotid artery could result in loss of consciousness. Indeed the word carotid is derived from the Greek, meaning to stupefy or plunge into a deep sleep. The early history of carotid surgery is limited to a small number of case reports by individual surgeons (many of whom were illustrious pioneers of their time), usually performing ligation as a life saving procedure post trauma, but also occasionally for the exclusion of a carotid aneurysm. Not surprisingly the success of the operations was variable, and peri - operative neurological insult not infrequent.

The early 20th century saw three great advances in the development toward carotid surgery for stroke; firstly Chiari in 1905 described the pathological features of the ulcerative atherosclerotic plaque and proposed the mechanism of emboli. Secondly Ramsay Hunt in 1914 described the association between cerebral infarction and partial or complete carotid occlusion. Lastly Egas Moniz in 1927 performed the first successful cerebral arteriogram, so paving the way for the investigation of stroke causation.
Although the association between stroke and carotid occlusion was noted by Hultquist[(2)] in his post - mortem study of 1942 the relation of TIA's with stenosis was not made until some ten years later. In Eastcott's[(3)] description and justification of his surgery for a lady with TIA's he poured scorn on the then current theories of "Chronic Pseudo - Uraemia" (Volhard 1931) and "Chronic Hypertensive Encephalopathy" (Oppenheimer and Fishburg 1928) where TIA's were thought to be related to isolated episodes of cerebral vasospasm. Although not attempting to define what the cause of TIA's, Eastcott raised the concept of two potential mechanisms; firstly that periods of hypotension for whatever cause in the presence of a tight stenosis may lead to hypoperfusion, hypoxia and symptoms. Secondly that Pickerings work in 1948 where the similarity between hypertensive TIA's and those of valvular heart disease/cardiac arrhythmia origin raised the potential of an embolic cause. With time the latter explanation has been found to be correct.

Fig 1.4. Carotid angiogram



Early Pioneers

Due to the unknown nature of the pathophysiology and the initial (incorrect) theory of cerebrovasospasm the first procedures that were performed were attempting to reduce vasospasm. Chao[4] in 1938 resected the vessel and Johnson and Walker[5] in 1951 performed a cervical sympathectomy, unsurprisingly these were not successful.

In 1951 the first successful surgical procedure for stroke was performed by Carrea[6] in Argentina. Here a stenosed internal carotid artery was partially resected and an external to internal carotid bypass fashioned.

In the same year the technique of thromboendarterectomy gained popularity in vascular surgery, initially for the aortoiliac segment. It was not until 1953 that the first thromboendarterectomy of a carotid was performed, unfortunately unsuccessfully due to presumed distal disease, by Strully[7]. This was followed a few months later by the first successful procedure by Michael De Bakey[8] on a patient with a frank stroke and total occlusion.

One of the most significant operations in carotid surgery took place in London in 1954 when Eastcott[3] performed the first procedure for transient ischaemic attacks in a lady with crescendo TIAs and a carotid stenosis demonstrated by direct puncture arteriography. General anaesthesia with hypothermia to 28^{o}C employed as a cerebral protective mechanism was used, without the use of an indwelling shunt. This procedure was initially planned to be resection of the effected segment and insertion of a graft, but due to the mobility of the vessels was in fact a common to internal carotid anastomosis.

The first reported use of a shunt was in 1956 when Cooley[9] performed a general anaesthetic endarterectomy with hypothermic cerebral protection for a 71 year old man with a persistent and disabling swishing noise in his left ear. The shunt used was not indwelling but rather a fearsome looking polyvinyl device with a 14 gauge cannula at one end and 16 gauge at the other. Cross clamp time was nine minutes during which the shunt was thought to function well. The patient awoke with no swishing noise but with a temporary right sided weakness of the hand.

With time and experience the various procedures (listed below in table 1) have been reduced to endarterectomy alone.

Development of transcranial Doppler has enabled surgeons to demonstrate the embolic load which we have presumed to be the cause of ischaemic events and to assess the improvement that occurs with an endarterectomy[10, 11]. This work has shown that the hypothesis that there is an embolic load, removable by surgery, is correct and justifies the performance of surgery. Additionally it has demonstrated that the embolic load reduces with time, in part explaining why patients who are symptomatic but not operated upon do not invariably progress on to stroke. This also justifies the current surgical approach of operating within six months of symptoms.

Table 1.1. Chronology of modern carotid procedures

AUTHOR	DATE	STENOSIS	PROCEDURE
Carrea, Molins, Murphy	20.10.51	Partial	End to end, external to internal
Strully, Hurwitt, Blankenberg	28.1.53	Total	Endarterectomy, ligation/resection
Debakey	7.8.53	Total	Endarterectomy
Eastcott, Pickering, Robb	19.5.54 &	Partial	End to end, common to internal
	2.6.54	Partial	Endarterectomy
Denman, Ehni, Duty	14.7.54	Total	Resection with homograft
Lin, Javid, Doyle	Dec 1955	Partial	Resection with saphenous vein graft
Murphy, Miller	6.2.56 &	Total	Endarterectomy
	24.2.56	Partial	Endarterectomy
Lyons, Galbraith	9.8.56	Partial	Subclavian – carotid nylon bypass

Jesse Thompson

Although no single person can be credited with the popularisation of this operation, Jesse Thompson of Dallas, Texas has probably made the biggest individual contribution. His publishing career spans three decades and includes a large number of invited reviews in major journals on both sides of the Atlantic[12 - 18].

He stratified patients into four categories of frank stroke, TIA's, asymptomatic and those with chronic cerebral ischaemia having recognised that each group had markedly different prognosis and complications and so were so not directly comparable. His follow up of outcome and use of control groups to identify the natural history of the disease has allowed him to make valued comment on which patients benefit from surgery and on how and when to operate. His commentaries have also reviewed new techniques in investigation of carotid stenosis with increasing emphasis on non invasive methods as they improved in accuracy during the late 1970's and into the 1980's. His preferred technique is to perform the operation under general anaesthesia with the mandatory use of an in dwelling shunt to maximise cerebral protection.

His complication rates of his reported personal series are excellent especially in his later cases having overcome the "learning curve". His mortality rate fell from 4.8% (272 operation between 1957 - 1963) to 1.5% (868 operations 1964 - 1975) with the highest risk patient subgroup being those with frank stroke and the lowest risk being those with asymptomatic stenosis. His contribution is therefore as both an excellent practitioner of the procedure and as a teacher.

Symptomatic disease

From the first successes in the 1950's surgeons began to perform endarterectomy with increasing frequency. The first randomised trials did not show a benefit from surgery but having discovered what they consider to be a good operation surgeons persisted and with experience complication rates fell.

The USA has a different healthcare system to that in Britain with many being required to have private health insurance or pay directly for services. Possibly as a consequence of this endarterectomy rates rose through the 1970's and early 1980's, from 15 000 in 1971 to a staggering 107 000 in 1985. At this high point several events occurred which caused a reduction in popularity; risk management/ life - style modification began to be addressed, antiplatelet therapy was shown to be of benefit and extracranial - intracranial bypass proven to be ineffective in preventing stroke. This spurred American surgeons to form the North American Symptomatic Carotid Endarterectomy Trial (NASCET) which began after the European Carotid Surgery Trial (ECST). The purpose of both these studies was to assess the efficacy of surgery against optimal medical care (including antiplatelet drugs) with follow up for two years and the inclusion of all peri operative complications.

NASCET

Commenced in 1988 and terminated in February 1991 for those with 70 - 99% stenosis, NASCET published its interim results in The New England Journal of Medicine in August 1991[19]. The trial was conducted in 50 US and Canadian centres who required a 30 day mortality and stroke rate of less than 6% in their last 50 endarterectomies performed within the previous 24 months to be eligible.

Patients under 80 years with TIA, amaurosis fugax or non - disabling stroke within the previous 120 days were eligible for recruitment in the presence of a 30 - 99% carotid stenosis. Informed consent was obtained.

Angiography was used to assess the degree of stenosis, with a radiologist equipped with a jewellers eyepiece marked in tenths of a millimetre calculating the stenosis from the ratio of the narrowest part of the lumen divided by the normal diameter beyond the carotid bulb (see fig 1.5)

Angiogram stenosis were classified as <30% (in which case they were sent for independent external adjudication), 30 - 69% or 70 - 99%. Angiograms were selected in 127 random cases and assessed by the principal neuroradiologist to ensure consistency (kappa = 0.89).

Upon enrolment all patients underwent a standardised series of tests including CT head and carotid duplex. Randomisation to medical therapy alone or medical therapy plus surgery was made by computer programme.

The aspirin dose was usually 1300mg. Surgery technique varied between individual surgeons. Simultaneous carotid/CABG and simultaneous bilateral endarterectomy were proscribed.

Follow up examination was performed by the surgeon at day 30 or at discharge, whichever occurred first. Neurological, medical and functional assessment took place one month after entry, then every three months for the first year and every four months thereafter. Duplex was performed one month after entry. CT head was performed in any suspected CVA, with angiography being used if clinically appropriate and duplex if the CVA was in the carotid territory.

Results were collected and review led to the trial being stopped early due to a statistically significant benefit in favour of surgery, $p < 0.001$ (see table 1.2 below)

Table 1.2. Summary of NASCET findings

Event defining failure	Medical (n = 331)	Surgical (n = 328)	% relative risk reduction
Any ipsilateral stroke	61 (26%)	26 (9%)	65
Any stroke	64 (27.6%)	34 (12.6%)	54
Any stroke or death	73 (32.3%)	41 (15.8%)	51
Major/fatal ipsilateral stroke	29 (13.1%)	8 (2.5%)	81
Any major/fatal stroke	29 (13.1%)	10 (3.7%)	72
Any major stroke/death	38 (18.1%)	19 (8%)	56

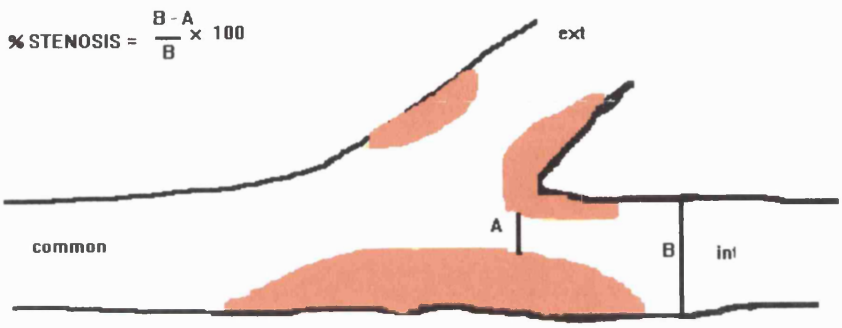
ECST

Commenced in 1981, the European Carotid Surgery Trial randomised its last patient in 1994, with follow up being terminated at the end of 1995 after a mean of 6.1 years. Its findings were published in May, 1998 in The Lancet[20]. The study was truly multi - national with ninety seven centres in twelve European countries and one in Australia taking part. The design was to compare the benefit of "carotid endarterectomy as soon as possible" with "avoid surgery if at all possible, for as long as possible".

Patients were eligible if they had experienced, in the previous six months, one or more carotid territory ischaemic events in the brain or eye, which were either transient (symptoms lasting either minutes, hours or days) or permanent but not causing any serious disability. Patients were excluded if they had cardiac focus of emboli or if the disease was more severe in the distal than proximal internal carotid.

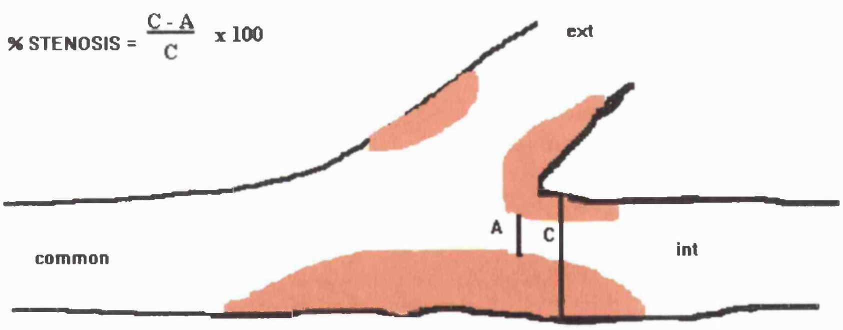
Angiography was used to determine the degree of carotid stenosis, with all angiograms being reviewed centrally by a single observer. As shown in the diagram below (fig 1.6), the denominator was an estimate of the original width of the artery unlike in NASCET where the denominator was the diameter of the distal ICA. If only one artery was symptomatic , this was defined as the symptomatic side. If both arteries were symptomatic then the side with the most recent symptoms was defined as symptomatic.

Fig 1.5. NASCET determination of carotid stenosis



NASCET method of assessment of carotid stenosis

Fig 1.6. ECST determination of carotid stenosis



ECST method of assessment of carotid stenosis

Randomisation was performed centrally by computer programme. Regardless of treatment allocation all patients received best medical management, i.e. anti platelet therapy, treatment of hypertension and advice against smoking. Allocation to surgery required the patient to receive their operation within a year of randomisation. After randomisation information was required at 4 months, 12 months and then yearly until the end of 1995. Due to potential for patients to have multiple complications/adverse outcomes, stroke was chosen as the main outcome measure.

Three thousand and twenty four patients were randomised; 1811 to surgery and 1213 to control. The mean follow up was 6.1 years. Only 25 patients were lost to follow up. Groups were fairly evenly matched although the surgical groups did have slightly more hypertensives and those with ischaemic heart disease. Control patients were also more likely to be prescribed anti - platelet therapy, anticoagulation and lipid lowering therapy (p = 0.003).

Sixty two (3.4%) of those in the surgery group did not receive their surgery within a year of randomisation. 5 patients had a major stroke whilst awaiting surgery.

One hundred and forty three (11.8%) of the control patients underwent carotid endarterectomy during the trial, with 42 receiving their operation within the first year and so included as part of the surgical group.

It was found that the stroke rate of the control group fell markedly after three years irrespective of original degree of stenosis. The mechanism by which this fall occurs is unknown but possibly may be due to plaque stabilisation.

Overall there was little difference between the two groups with major stroke rates of 17.4% in the surgical group and 17.8% in the control, but with stratification for degree of stenosis at presentation a benefit from surgery occurred in the range 70 - 79% stenosis. This benefit continued up to 99% stenosis. The authors concluded that the 80% stenosis in ECST is equivalent to 70% in NASCET due to the slightly different methods used and the agreement between the two trial strengthened the argument for surgery.

The benefit from surgery was 11.6%, i.e. 116 major strokes or death are avoided per 1000 operations. This means nine patients require surgery to avoid one stroke, if major disabling strokes are used as a criteria this rises to eighteen operations required.

Further analysis of the data by age, gender and stenosis have produced treatment curves to assist in decision making for individual patients. As a general rule, men require a lower degree of stenosis than women to obtain benefit and younger people should be operated on for lesser degrees than older people.

Conversion of ECST and NASCET figures

Although both NASCET and ECST used angiography as the method of investigation of the carotid artery different points were used to calculate the degree of stenosis and so results are not directly equivalent. To assist in the interpretation of the two papers a correction factor has been produced[21]:

% stenosis by ECST = (0.6 x % stenosis by NASCET) + 40%

A direct conversion is listed in the table 3.

Table 3. Approximate conversion from NASCET to ECST

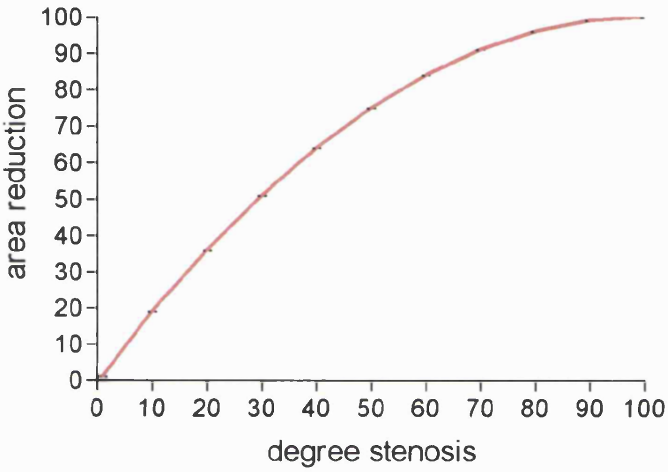
NASCET (%)	ECST (%)
30	65
40	70
50	75
60	80
70	85
80	91
90	97

Relationship of vessel diameter to area

Luminal area is related to diameter by the formula Area = πr^2

The effect of this formula is to give a non linear relationship between area and diameter (see fig 1.7) and results in a 70% reduction in diameter creating a 92% reduction in luminal area[22]

fig 1.7. Effect of degree of stenosis on luminal area



Conclusions raised from NASCET and ECST

Carotid endarterectomy should be performed in centres with low complication rates and offered to patients with a symptomatic high grade stenosis provided that their symptoms were recent, i.e.within six months.

Surgery for Asymptomatic disease

Since endarterectomy can reduce the risk of a further embolic cerebrovascular injury in those with a symptomatic high grade stenosis it would seem logical that it may have a role in prophylaxis for those who are asymptomatic with a high grade stenosis. Two trials have attempted to answer this question in recent years; the Asymptomatic Carotid Atherosclerosis Study (ACAS, North America)[23] and The Asymptomatic Carotid Surgery Trial (ACST, Europe)[25].

ACAS

Commenced in December 1987 and terminating in December 1993, ACAS reported in May 1995. Thirty nine centres were chosen from an applicant pool of fifty five. Study participants were recruited from ultrasound vascular laboratories, practitioners who auscultated asymptomatic carotid bruits and practitioners identifying carotid stenosis in patients under investigation with other vascular diseases.

Inclusion criteria were age 40 - 79 years, willingness and accessibility for the five year follow up, performance of ECG and other investigation no earlier than three months prior to randomisation and a compatible history and physical examination. Informed consent was obtained. Patients were excluded if they had neurological symptoms in the territory of the study carotid artery or vertebrobasilar system, symptoms referable to the contralateral cerebral system within the previous 45 days, contraindication to aspirin therapy, a disorder that could seriously complicate surgery or a condition likely to lead to death or disability within the five year study period.

Significant stenosis required one of three criteria to be met: arteriography within the previous 60 days showing a stenosis of greater than or equal to 60% reduction in diameter (if angio was performed 61 - 364 days prior to randomisation and showed significant stenosis, a patent artery demonstrated on doppler was accepted); Doppler examination within the previous 60 days showing frequency or velocity greater than the instrument specific cut point with 95% positive predictive value; or lastly Doppler examination showing a frequency or velocity greater than the instrument positive predictive value cut - off point confirmed by oculo pneumoplethysmographic examination within 60 days.

The degree of stenosis was calculated by dividing the smallest lumen diameter at the site of the stenotic lesion (minimal residual lumen, MRL) by the diameter of the internal carotid distal to the stenosis at which the vessel walls became parallel (distal lumen, DL) and placing the figures into the below calculation:

% stenosis = 100 x (1 - {MRL/DL})

Once approved by both an ACAS surgeon and neurologist as suitable the patients were randomised using a computerised programme held at the statistical co-ordinating centre. All patients had advice regarding lifestyle modification and received 325mg aspirin daily. Those recruited into the surgical arm were scheduled to receive surgery within two weeks of randomisation and received an arteriogram and CT if not already performed.
Patients were evaluated by the surgeon, ACAS neurologist and the ACAS patient co-ordinator 24 hours post surgery. Thereafter follow up occurred at one month and then every three months, with alternate clinic visits and telephone contacts. Doppler assessment of the carotid occurred at three months, six monthly for 24 months and then yearly until exit from the trial, when a CT was also taken.
The mean follow up was not the full five years as one would expect , but rather a mean of 2.7 years. Use of Kaplan - Meier life tables allows an estimation of the differences at five years, although this is based in favour of medical therapy since most surgical complication arise within 30 days of surgery. The advantage of surgery could further be increased if non - invasive assessment of carotid stenosis rather than arteriography were employed since the neurological complication rate of this alone was 1.2%. Despite these two confounding factors surgery appears to give a statistically significant reduction in stroke or death when compared to medical therapy

Table 4. Summary of ACAS findings

Event	**Medical**	**(n = 834)**	**Surgical**	**(n = 825)**	**Risk reduction**
	Observed 2.7yr	**Estimated 5yr**	**Observed 2.7yr**	**Estimated 5yr**	
Ipsilateral stroke Perioperative stroke Death	52	92 (11%)	33	42 (5.1%)	0.53*

*p < 0.004

ACST

The Asymptomatic Carotid Surgery Trial is still ongoing but has already recruited more patients than any other trial of carotid endarterectomy in asymptomatic patients. The purpose of the trial is to determine the best treatment for those with asymptomatic carotid stenosis by comparing surgery with best medical management. It has recruited 1660 patients to date and involves 127 centres in 25 countries, most of which are in Western Europe[22]. As with ACAS centres are asked to participate if they have a low (<3%) peri - operative complication rate. It differs significantly from all previous major trials of carotid surgery since angiography is not used to determine the degree of carotid stenosis for randomisation, instead duplex is used. All the vascular laboratories in the trial have been validated, either against angiography or against en bloc carotid specimens although a variety of equipment and insonation angles have been used.

By using duplex to randomise patients the trial organisers hope to achieve two things. Firstly to represent the move toward non invasive carotid assessment which has been seen in the last decade with the development of better duplex systems, and secondly to remove the angiographic complications from the overall figures and so give a better indication of the potential benefit of intervention.

If the results reinforce those of ACAS then the case in both symptomatic and asymptomatic patients will have been proven, but providers will have to bear in mind the need for very low peri - operative complications to retain the benefit of the original trials.

Other data

NASCET was established to demonstrate whether symptomatic carotid disease required surgery and if so at what degree of stenosis. In investigating the trial participants a large number of asymptomatic stenosis were discovered which have now been rigorously followed up. Reported in June 2000[26] in the New England Journal of Medicine the triallists had followed up 1820 patients for five years. 1604 had a stenosis less than 60% and 216 greater than 60%, the lesser degree of stenosis being associated with a 1.6% annual stroke rate (8% over five years) and the higher degree with double that risk at 3.2% annually (16.2% over five years). Initially this would appear to be a significant risk and reinforce the argument for surgery, but dividing the strokes by causation into large vessel, lacunar and cardioembolic did not support this. For those in the 60 - 99% stenosis study group the risk of a stroke over the five year period in the territory of a large vessel was 9.9%, of lacunar stroke was 6% and of cardioembolic stroke was 2.1%, i.e. the study revealed that only 55% of the total strokes were large vessel strokes which could be prevented by surgery. Interestingly the annualised risk of stroke in those with high grade stenosis was only marginally higher than the 86 patients in the subgroup with an asymptomatic occluded artery (1.98% vs 1.9%) for whom surgery cannot be considered. They calculated that 116 operations would be needed to prevent one large vessel stroke. Although not ruling out surgery for asymptomatic disease the authors urged caution since their data would indicate that the presence of an asymptomatic high grade stenosis only confers a relatively small chance of a large vessel territory stroke, which to prevent would require a large number of operations to be performed.

Open versus Endovascular Surgery

Endovascular surgery has become increasingly part of vascular practice in the last decade; angioplasty of the femoral vessels has markedly reduced the need for fem - pop bypass and aortic stenting is now being performed in a large number of centres world-wide. Due to this increase in use of angioplasty and stent techniques in other vessels, attention turned to the carotid vessels earlier in the 1990's. A recent review[27] of the subject by one of the most prominent interventional radiologists demonstrated that their is a great deal of enthusiasm for the technique world wide, not least because of the perceived benefits of a shorter hospital stay when compared to surgery (2 - 4 days vs 7.1 days) and the potential for product, especially memory alloy stents, development. The technique is currently being refined with the introduction of custom made distal occlusion balloons and catheters that can aspirate debris, but no ideal system is available. At Dr Gaines' review there were four published series of carotid angioplasty/stenting in addition to his own series of 108. These series involve a total of 638 procedures with a death/stroke rate varying from 0.8% - 5.6%, with the majority being for symptomatic high grade stenosis.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) reported its results at the Vascular Surgery Society in November 1998[28]. This study was performed in 24 centres in Europe, Australia, Canada and the USA. 504 patients were randomised between 1992 and 1997. Mean age was 67 years with 69% being male. 90% were recently symptomatic and mean stenosis was 87%. 253 were randomised to surgery and 251 to angioplasty. Thirty day disabling stroke and death rates are similar at 6.3% in the surgery group and 6.4% in the angioplasty group. Cranial nerve injury and myocardial events were restricted to the surgery group. The investigators conclude that this demonstrates that angioplasty is as safe as surgery.

At presentation this paper caused lot of debate, primarily because of the high complication rates, which are actually higher than those used as the entry criteria for units to take part in NASCET. The reply from the speaker was that the patients in CAVATAS were examined by neurologists rather than surgeons leading to the detection of lesser degrees of neurological deficit which would probably not have been noted by the surgical team.

At the publication of the full trial in 2001[29] the accompanying commentary[30] expressed concern at the complication, stroke and death rates of both angioplasty and operative surgery which were higher than those reported in both NASCET and ECST. The commentators felt this may have reflected a truer picture of current clinical practice and outcome rather than poor practice in the participating centres. They concluded that stenting did not have a place in the management of either symptomatic or asymptomatic disease but could have a place in the management of those not suitable for open surgery due to lack of fitness or hostile anatomy (previous neck exploration, radiotherapy etc). The combination of cost, limited benefit over open surgery and paucity of trained interventional radiologists familiar with the technique is likely to mean that carotid stenting will continue to be performed in a relatively small number of specialised centres as part of a trial rather than being performed on a widespread basis. As with many new techniques there is a great deal of enthusiasm for carotid stenting and the technology has improved with smaller catheters and cerebral protection devices. Currently two further trials are enrolling patients; the Stent – protected Percutaneous Angioplasty of the Carotid artery with Endarterectomy trial (SPACE) and the International Carotid Stenting Study (ICSS). SPACE is based in Germany and Austria and has recruited 223 patients in 16 centres. It is anticipated that 1900 patients will be required and that 30 centres will be involved. ICSS has also been called CAVATAS II and has randomized 54 patients in 12 centres.

ACE

The Acetylsalicylic Acid (ASA) and Carotid Endarterectomy Trial (ACE) ran from July 1994 until April 1998 and reported in The Lancet in 1999[32]. The stimulus for the study was post hoc reports of varying mortality in different doses of acetylsalicylic acid (aspirin) for those in NASCET[33], with high dose doing better than low dose. This did seem contradictory to the accepted pharmacological properties of aspirin, which in lose dose suppresses Thromboxane A2 and so reduces platelet aggregation, but in high doses suppresses the antiaggregant prostacyclin and so increases thrombosis. The ACE trial was designed to answer what effect, if any, the dose of aspirin had on morbidity and mortality post carotid endarterectomy, with no placebo group being used due to ethical considerations.

Seventy four centres world wide participated all with a 30 day stroke and death rate of <6%. Patients were excluded if they could not take 1300mg of aspirin daily, were on other anti – platelet medication, were in another trial, had received cardiac surgery in the preceding 30 days, were to receive cardiac surgery in the next 30 days, had a recent disabling stroke or were not able to give consent. Randomisation was done by computer, with stratification by centre and balancing every 12 patients. Kits containing blister packs of tablets were sent out form the coordinating centre in Ontario to each centre. Each pack contained seven rows of five tablets, a mixture of placebos and different doses of aspirin, with patients instructed to take five tablets per day for a week. The daily doses were either 81mg, 325mg, 650mg or 1300mg.

2849 patients were recruited, with 2804 being available for 30 day and 3 month follow up. The groups were almost equal (81mg = 698, 325mg = 697, 650mg = 703, 1300mg = 706) and patient characteristics similar.

Analysis was done in two ways; all patients and an efficacy analysis where those on aspirin doses >650mg/day pre – entry in the trial were removed.

In the whole group analysis the only stastical significant difference was at 3 months where the low dose group performed better than high dose when comparing any stroke, MI or death, 6.2% vs 8.4%, $p = 0.03$.

When analysed on an efficacy basis (where pre – operative aspirin dose taken into account) the low dose group was significantly better than high dose at both 30 days and 3 months when looking at the categories any stroke MI or death; any stroke or death; ipsilateral stroke or death.

The number of haemorrhagic strokes was similar in all four aspirin doses as was the rate of gastrointestinal upset, so it would appear that the effect that the doses of aspirin are having is not through raising the risk profile of bleeding or peptic ulceration but rather through an effect on the potential for thrombosis or embolisation.

The authors recommend that the findings of the post hoc analysis in NASCET should be ignored and that patients should be treated with low dose aspirin in order to reduce the post operative MI, stroke and death rate post carotid endarterectomy.

The future

All the trials described in the earlier part of this chapter are an accurate representation of surgery versus best medical management as it was available in the 1980's and early 1990's. Since then there have been several advances in cardiovascular therapeutics, most often with the intention of improving cardiac morbidity and mortality but with significant additional effects in peripheral and central vascular disease. This does not invalidate the trials or change the accepted threshold for surgery at present, but it may be that over the coming decades there will need to be a reassessment.

Statins are a family of agents which lower low density lipoprotein cholesterol (LDL's) by their action on 3 – hydroxy – 3 – methyl – glutaryl – coenzyme A (HMG – CoA) reductase, an enzyme in the endogenous production of cholesterol. In a large number of trials they have demonstrated their ability to lower serum cholesterol and this has been translated into clinical effectiveness by alteration in both outcomes of all atherosclerotic related morbidity and mortality(34 - 36) and by stabilization of plaques(38), these effects being independent of baseline serum cholesterol. The consensus feeling of many vascular surgeons in both the UK and abroad is that patients with arterial disease should be offered a statin, regardless of serum cholesterol.

Blood pressure control and reduction of risk of cardiovascular mortality has been shown in placebo controlled trials, although which antihypertensive should be used, either alone or in combination, is less clear(39 - 45). Newer classes such as the Angiotension converting enzyme II are showing even more promise, but what place these (expensive) drugs will have is yet to be defined.

The anti – platelet agent used in the ECST and NASCET trials was aspirin, a well known and phenomenally cheap agent. Since then a new class of anti – platelet agent, the glycoprotein IIb/IIIa inhibitors, has come into useage. The initial agent, Ticlodipine, was associated with the serious side effect of bone marrow suppression which made clinicians reluctant to use it. Further development produced an isomer, Clopidogrel, which has a much better profile without a significant reduction in beneficial effects(46). Used alone it is superior to aspirin, but much more expensive[47], and even more effective when used in combination[48]. As time passes more patients are being prescribed Clopidogrel which may translate into alteration in the embolic load patients suffer and a reduction in the incidence of TIA's and strokes.

Improvement in the medical management may reduce the number of patients who require surgery, but there will still be a need for endarterectomy. The current complication rates of <5% are commendable, but a further reduction should be the aim of all surgeons. Duplex technology has improved and it may be that with a combination of improved imaging and data analysis that it will be possible to identify which plaques are high risk for embolisation and therefore stroke either pre – or peri – operatively[49].
Complications appear to be related to surgical experience[50] with surgeons who perform <10 cases per year having higher complications, leading the authors of the paper to conclude that surgery should be performed in specialist high volume centres.
The operation itself has four potential major differences when comparing surgical centres; it can be performed under locoregional or general anesthesia, by a standard or eversion technique. There is some evidence that locoregional anaesthesia is preferable[51 - 53], but the ongoing GALA trial will hopefully formally address this. Eversion endarterectomy may be easier to perform[54] with much interest on continental Europe but has yet to find a firm foothold in the UK.

1.iii Methods of Investigation

Since the first angiograms of the 1920's investigation of the extra and intracranial circulatory tree has become much more sophisticated and in the last two decades good quality non invasive imaging has become available.

Early angiography relied upon direct puncture techniques which limited the number of vessels investigated at one sitting and also meant directly needling the diseased vessel under question with the risk of dislodging plaque/debris. The angiographic technique now in use utilises the femoral or brachial artery as the route of insertion with passage of a catheter over guidewire to selectively enter the vertebral and carotid vessels. It is not always necessary to image all four vessels. With good quality X ray equipment connected to computers loaded with the correct software to subtract the bony skeleton (digital subtraction angiography, DSA) one can obtain very good images of the arterial tree. Despite the quality of the images obtained and the use of a distal insertion site, angiography is still associated with a 0.3 - 1% stroke rate[23, 24, 28] with recent data[31] suggesting that cerebral angiography where the common or internal carotid is utilized is associated with an overall 23% rate of MRI detected microemboli, but with arteriopaths being at much higher risk than non arteriopaths (44% vs 13%). Although this complication rate is low it has created a need for alternative methods of assessing the degree of stenosis. Intravenous DSA can be used to image the arterial tree, but the images are not as good as those obtained by either selective angiography or intra arterial DSA.

Hand held doppler can be used to insonate the vessels of the neck but is operator dependant and totally subjective. Insonation of the supraorbital vessels to identify reverse flow may indicate impending ICA occlusion and be used as an indication for urgent surgery

Oculoplethysmography (OPG) can be used to assess the degree of internal carotid stenosis and the adequacy of the collateral supply[13]. Two methods have been applied, named after their investigators. OPG - Gee measures opthalmic artery pressure and when accompanied by carotid compression gives an estimate of stump pressure. OPG - Kartchner compress the ocular waveform in the two eyes to assess the presence and significance of ICA lesions. Carotid compression is not used. Compared with arteriography OPG - Kartchner gave 87% accuracy.

Duplex scanning has revolutionised non invasive carotid assessment
since it can investigate the extracranial vessels for degree of stenosis, can identify situations of "trickle flow" through very tight lesions, can attempt to make a judgement on plaque morphology, is portable enough to be used in theatre for quality control and is very acceptable to patients. The main disadvantage is the capital cost of buying the machinery and the need for highly trained operator, be they surgeon, radiologist, physicist or vascular technician. The technique has been validated against angiography in both the great vessels of the neck and the peripheral vasculature, and indeed is now being used as the method of randomisation to the ACST[25, 55-58]. Individual units need to ensure that continually audit their scans to ensure quality control, but provided this standard is maintained duplex will remain an integral part of vascular assessment.

Magnetic resonance angiography (MRA) is a non invasive technique which uses a large magnetic field rather than radiation to investigate tissues. It therefore has the dual advantage of avoiding arterial catheterisation and potential emboli without exposing patients to high doses of x - rays. Early scanners has the disadvantage of long (> 10 minutes) scan times and variable image quality. As technology has improved scan speeds have decreased to 30 seconds and with the advent of digital subtraction (MRDSA) image quality has increased[59- 61]. This had led several authors to promote the use of duplex ultrasound in combination with MRA to avoid angiography[62, 63]. As availability of good quality MRA increases this may become the case.

1.v Quality Control

Technical faults can occur in any type of surgery and these may give rise to post operative complications which vary in magnitude of severity from minor to fatal. Carotid surgery is not immune to this phenomena, but suffers from the disadvantage that the end organ is the brain which does not tolerate injury very well. This had led to some practioners[64 – 69] to promote a period of quality control examination of the completed endarterectomy. The systems recommended include duplex imaging, angioscopy and arteriography. The purpose is to detect any flaps or significant stenosis which have been missed by the operator and allow their correction.

Not all defects are considered significant to warrant re – exploration, but distal flaps and severe residual stenosis > 70% are considered worthy of exploration when identified by duplex[64 - 66], whilst those using angioscopy[67, 68] can detect residual flaps and adherent thrombus which again require exploration. What effect these defects would have had on the patients is unknown, but the presumption is that the flaps would either have been a focus for embolisation or would lift up and occlude the internal carotid and so once identified the operator re – explores the artery and corrects them. Leaving a stenosis of > 70% may be acceptable[65], but this does seem an odd action since one would have been operating to remove a significant stenosis. Follow up of these patients[69] has shown that the stenosis may progress, but that they do not appear to cause either symptoms or strokes, possibly because the lining of the artery is no longer a thrombogenic atherosclerotic plaque and so less likely to embolise.

Despite the fact that the above studies have shown technical defects in 3- 6% of patients many centers do not perform quality control and have similar outcomes and complication rates as those that do. In view of this present lack of evidence no firm recommendation can be given as to the need for quality control.

1.iv Cerebral Protection

Cerebral protection by physiological or pharmacological methods has been employed in both carotid and cardiac surgery. The early pioneers often used hypothermia for this with the hypothesis that at reduced temperature the metabolic demands of tissue becomes minimal and so neurones will survive the period of potential ischaemia[3]. The disadvantage of this is the real danger of myocardial irritability secondary to cold which is extremely difficult to control and is refractory to pharmacological intervention until the patient is warm. As other methods have become available hypothermia has largely been replaced, although it is still used in developing countries to assist in cardiac surgery.

General anaesthesia causes a reduction in cerebral metabolism and sodium thiopentone was the favoured anaesthetic for a long time due to its perceived protective effect on neurones. Despite this the cross clamp time to perform a satisfactory endarterectomy is such that in the presence of an inadequate collateral circulation damage to neurones will almost certainly occur.

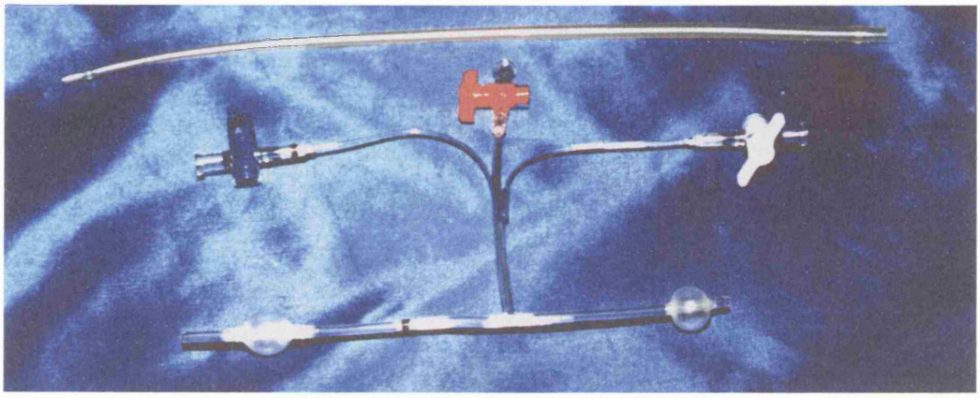
Pharmacological intervention in trauma has only been shown to be of benefit in animal studies when given prior to injury [70], but the mechanism of injury here is cell death and oedema related to a blow rather than hypoxia and so is unlikely to be applicable to patients with diffuse atherosclerosis receiving endarterectomy.

The only thing which would appear to be of benefit is the restoration of blood flow to the brain, which can be achieved with a shunt. The early shunts were fearsome devices with cannulae at either end[9], whereas modern shunts are made of silicon and lie intraluminally. There are several different models available commercially but the basic design is of a smooth ended flexible tube which can held in place with either clamps or balloons and allows blood to flow from proximal to distal.

Assessment of the need to insert a shunt is simple in those who are under a locoregional anaesthetic since they are awake, but in those under general anaesthesia this is much more difficult. Several authors, notably Jesse Thompson, would recommend the mandatory use of shunt since they feel that in their hands insertion is not difficult and is not associated with iatrogenic complications. This argument is not universally accepted and has led to the development of a number of monitors of cerebral perfusion, including near - infrared spectroscopy, to assess the effect of cross clamp and allow shunts to be used selectively.

Regardless of opinion, all surgeons would agree that a shunt is at present the only way to restore perfusion to an anoxic brain until formal reperfusion post endarterectomy is achieved.

Fig 1.8. Carotid shunt



1.vi Other Operations

Aneurysms of the carotid artery are rare, accounting for approximately 0.5% of all carotid procedures. They are seen more frequently in females, with onset being from middle age onward. True aneurysms can be fusiform, saccular or mycotic (usually Staph Aureus) and with increasing frequency of other types of carotid surgery the most common form is the false aneurysm. Treatment is excision with either primary anastomosis or interposition grafting. The first recorded treatment of a carotid aneurysm was by Astley Cooper in 1808 who ligated a painful left common carotid aneurysm in a 50 year old man. The patient survived the procedure with resolution of his pain but with transient hoarseness of voice and drooping of the eyelid. Ligation would not be the treatment of choice today

Carotid body tumours are rare, with the highest incidence being seen in populations living chronically at high altitude with the subsequent hypertrophy of the carotid body. The tumour tends to grow up and around the internal and external carotid, giving a classic "goblet shape" on angiography. Treatment is by excision +/- post operative radiotherapy, but due to its vascularity excision can be a very difficult procedure.

Trauma is fortunately rarely seen in the UK, but is very common in countries such as South Africa and the USA. Mechanism of injury is usually related to penetrating with knives or gunshot, although blunt trauma and flexion/extension injuries can cause intimal damage and thrombosis. Treatment is initially resuscitation and control of haemorrhage followed by investigation and repair.

Summary

Carotid compression leading to cerebral insufficiency has been recognised since ancient times but it has only been in the twentieth century that science and medicine has advanced to give us a better understanding of the pathophysiological processes. Carotid endarterectomy is a relatively new procedure which has been subject to controversy due to early high complication rates and inappropriate over application. These problems have been partially addressed by multi - centre trials in both Europe and North America which have defined criteria for those who should receive surgery in those with symptomatic and asymptomatic stenosis, with clear benefit for those receiving surgery for a high grade recently symptomatic stenosis. Alternative intervention with carotid stenting has not as yet proven to confer any benefit and should remain within the confines of a trial at the present moment.

Chapter 2 Cerebral Monitoring and Shunts

2.i Introduction

As with most vascular procedures, carotid surgery requires the operating surgeon to apply clamps to stop in - flow and back - bleeding. In the unique situation of the cerebral vasculature this may lead to neurological deterioration. The mechanism for deterioration is related to decreased flow and hypoxia, possibly due to an incomplete Circle of Willis. With the development of the carotid shunt by Cooley(9) in 1956 came a way in which surgeons could potentially protect the cerebral vasculature from the detrimental effects of cross clamping by reducing the time of flow cessation to a few minutes at shunt insertion and removal. Under locoregional anaesthesia it is a simple matter to assess the patient's condition at cross clamping and insert a shunt if necessary with assessment of patency by improvement in clinical condition; most surgeons who perform endarterectomy by this method have similar figures to Steed's(71) report of 1982 where only 4% required shunting. With general anaesthesia this cannot be done leading to three alternative views on the matter; to always use an indwelling shunt, to never use an indwelling shunt or to selectively shunt on the basis of either pre - operative criteria, intra - operative criteria or a combination of both.

2.ii Shunt design and flow

Cooley's first shunt was simply a piece of polyvinyl tubing with a needle at either end, which looked rather fearsome. With time design has improved so that modern shunts are made of soft, pliable silicon which are inserted proximally and distally via the endarterectomy site and are held in place by either clamps or balloons. They are commercially produced, of good quality, sterile and can either lie solely in the endarterectomy site (intraluminal) or lie partially outside (extraluminal). For individual shunts flow rates are dependant on blood pressure, with hypotension being associated with reduced flow and hypertension with increased flow. The flow rate through a luminal structure obeys Poiseuilles' law:

$$\frac{(P_1 - P_2)\, \pi\, 60\, R^4}{8\mu L}$$

Where:

$P_1 - P_2$ = pressure gradient across the shunt

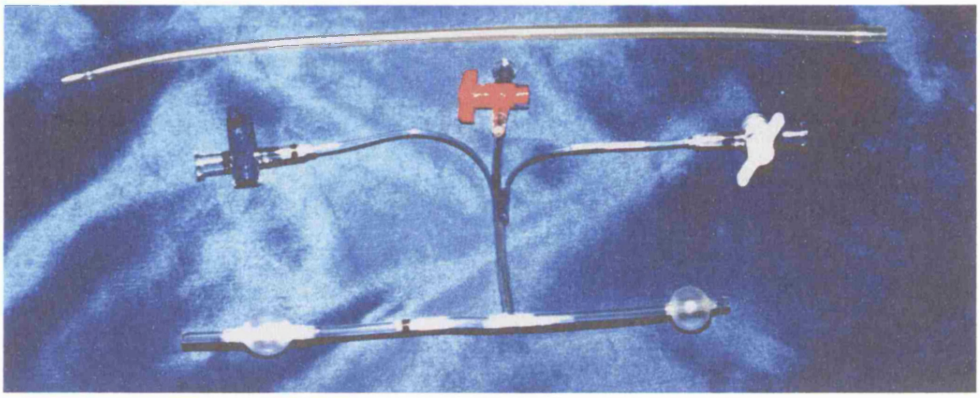
R = radius of shunt lumen

μ = viscosity of blood

L = length of shunt

Flow is therefore dependant on the fourth power of the intraluminal radius. This means that shunts of similar external diameter but of differing wall thickness will have different flow rates, and that shunts which have a balloon built into their wall will tend to have lower flow than those who do not. The flow through the shunt can be assessed by a flow meter[72 - 75] and when comparing a clamp held Javid shunt with a balloon held Pruit - Inahara (see diagram 2.1) shunt Beard et al[72] found that both on a bench test and in - vivo that the flow through the smaller Pruit shunt was statistically lower the Javid and that the flow achieved by the Pruit may not be sufficient to provide cerebral tissue with an adequate supply. Despite this it is still used by many surgeons.

Fig 2.1. Javid and Pruit Inahara shunts



Shunt use is not without disadvantage which is why not everyone agrees with their mandatory use[78]. Intimal flaps can be created during insertion which, if distal, have the potential to occlude the vessel; shunts may be a focus of emboli, and as already stated flow may not be sufficient to avoid cerebral hypoxia. Additionally whatever design of shunt is employed they tend to obstruct the surgical field and can be dislodged with an attendant period of cerebral ischaemia and blood loss. Lastly the distal ICA of some women is too small to accept even the smallest shunt.

2.iii Mandatory shunting

Always using a shunt has several attractive features; firstly it removes any uncertainty regarding the adequacy of cerebral supply, secondly it trains the surgeon to be familiar with the technique for times of crisis when speed is of essence. Thirdly it may brace the vessel to make it easier to suture. Additional advantages are that under general anaesthesia one does not have the patient's level of consciousness as a marker of cerebral function and would require some form of (often expensive) monitoring to allow selective shunting. Lastly, when teaching trainee surgeons who will initially be slower at endarterectomy it may be comforting for the supervising surgeon to have a shunt in situ.

The most famous champion of the shunt is Jesse Thompson[12 - 18] who feels that for the above reasons it should always be used. His view is shared by others[13, 76, 77] in both Europe and North America and his excellent series with low complication rates is a fairly powerful endorsement of this approach.

2.iv Non shunting

Despite Thompson's belief that the presence of a shunt did not increase the difficulty of the operation, others have shown that it does increase the time taken to complete the endarterectomy and that technical problems do occur with insertion and with maintenance of adequate flow[(79 - 82)].

There is also controversy over what degree of influence shunts will have on complication rates since series under locoregional anaesthesia (where the absolute gold standard of patient function is used as indicator for shunt insertion) patients have had peri - operative strokes/neurological deficit which were not related to hypo perfusion at cross clamping but probably were related to emboli, technical defects, reperfusion injury and intra cranial bleeds. Reported series in which a shunt is never used have complication rates which vary from mortality of 0.6% - 6.8% and morbidity of 4% - 9%[(79 - 81)]. The largest series in this group is by Baker, who subsequently changed his practice (see below) to non shunting of most but mandatory shunting of those with an occluded contralateral carotid.

2.v Selective shunting: patient presentation

Prediction of patients who will require a shunt at cross clamping cannot be made solely from clinical history or examination, but pre - operative investigations may be able to give a guide and are described in the following section.

As previously mentioned, Baker[81] did not routinely use a shunt but found that an occluded contralateral carotid trebled complication rates and changed his practice of mandatory non shunting to one where these patients did receive a shunt.

Blohme et al[83] have noted that the lowest rate of complications in their study of 272 consecutive endarterectomies was in those who had retinal symptoms only, with the highest being in those with presence of a cortical infarct on CT scanning and stroke as the presenting complaint. Although this is of great interest it suffers from the flaw that not all patients have a CT scan prior to their operation and so will not be universally applicable.

2.vi Selective shunting: Pre - operative assessment

Pre operative carotid compression to assess effect of occlusion can be employed but has several problems; firstly there is risk of dislodging friable plaque with resultant embolisation and secondly it is difficult to assess whether occlusion has caused cessation of flow.

Cerebral vasoreactivity and reserve[84 - 86] can be assessed by the method of CO_2 reactivity. This involves insonation of the ipsilateral middle cerebral artery with a transcranial doppler whilst the patient breathes air and then an air/5% CO_2 mix or receives an intravenous injection of 1g of acetazolamide (a carbonic anhydrase inhibitor)[87]. This should cause immediate and profound dilatation of the cerebral vasculature. If the cerebral vessels are already maximally dilated due to being in a constant hypoxic state or are diseased then there will be minimal change in the TCD trace, indicating that at clamping there will be no more reserve and so will not have the capacity to dilate further and increase cross flow, leading to the need for a shunt.

2.vii Selective shunting: Intra - operative monitoring

The last three decades have seen the utilisation of several different monitoring systems which measure either blood flow, blood pressure, electrical activity or tissue oxygenation to assess patients intra - operatively. Each of them has different merits and flaws but as yet none has proven to universally applicable with 100% specificity and sensitivity. Although predominantly used for the detection of cerebral hypoxia at cross clamping some systems can be used to assess shunt patency, detect emboli directly or indirectly and assess the adequacy of flow restoration at clamp release.

2.viii Monitors 1: Blood Pressure

Stump pressure is commonly used since it is easy to perform and does not require any costly equipment or the need for a technician. The technique (see fig 2.2a and 2.2b) is performed after the carotid sheath has been dissected and the internal and external branches well displayed. A small gauge needle connected to a manometer or pressure transducer is placed into the External Carotid just distal to the bifurcation, and clamps applied to both the External superior to the needle and the Common Carotid.

This will have the effect of stopping inflow from the heart via the Common Carotid and also any backflow from the well perfused face via the External Carotid. The pressure recorded should be the equivalent of the backflow down the Internal Carotid which is dependant on the patency of the Circle of Willis and the perfusion in the rest of the brain. A pressure level <50mmHg is used by most as an indication that the collateral supply is inadequate and that a shunt should be inserted. This technique although attractive because of its simplicity is not without problems because the stump pressure measurements do not correlate well with other forms of intra cerebral monitor[88, 89], and cannot be said to be reliable since Beebe[90] in 1989 showed that when measured serially in haemodynamically constant patients 20% would vary significantly from baseline. Under locoregional blockade stump pressure remains >50mmHg in 5% of those who become clinically compromised[91], but as mentioned earlier this may be due to these patients having an embolic rather than hypoxic injury.

When compared with transcranial doppler (TCD) stump pressure performs poorly[92, 93] in all but one trial by Spencer et al in 1992[94] where they used percentage change in middle cerebral artery flow versus stump pressure and analysed the data by best fit exponential function to give an correlation coefficient (r value) of 0.85. This is obviously of some concern from a haemodynamic perspective since the back (stump) pressure should be related to flow in the Circle of Willis which is being measured by TCD, if they rarely correlate then one must assume that the pressure is not solely flow dependant and so treat any measurement with caution.

In an effort to improve the accuracy some operators use stump index[95] which relates stump pressure to the systemic blood pressure, where:

Stump index = (stump pressure/mean systemic blood pressure) x 100

Published work with stump index appears to indicate that the distribution of stump index is more Gaussian than stump pressure, with a value of 40 and above being associated with adequate perfusion. Despite this the peri operative stroke rate in patients with an index value of >40 was still 1.1%, but again these may emboli related.

The current conclusion for both stump pressure and index is that although cheap and simple to perform it gives at best very limited information which has to be interpreted with care, and obviously cannot demonstrate emboli. As such neither stump pressure nor stump index can be recommended as a solitary indicator of cerebral perfusion intra operatively.

Fig 2.2a Clinical picture of stump pressure recording

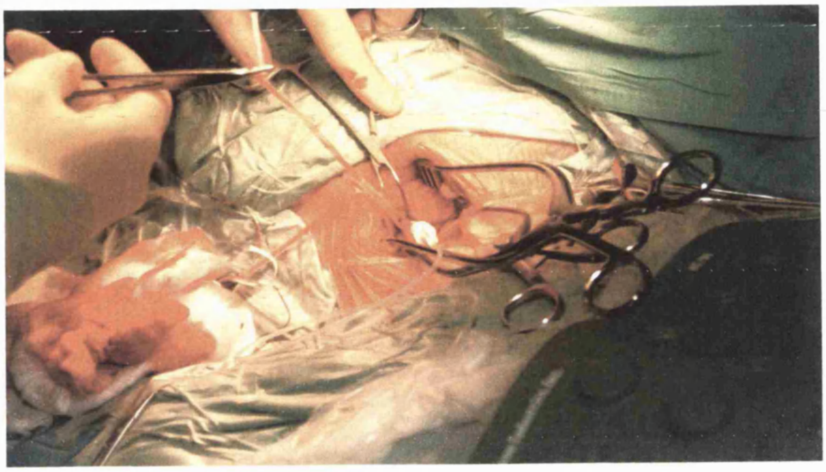
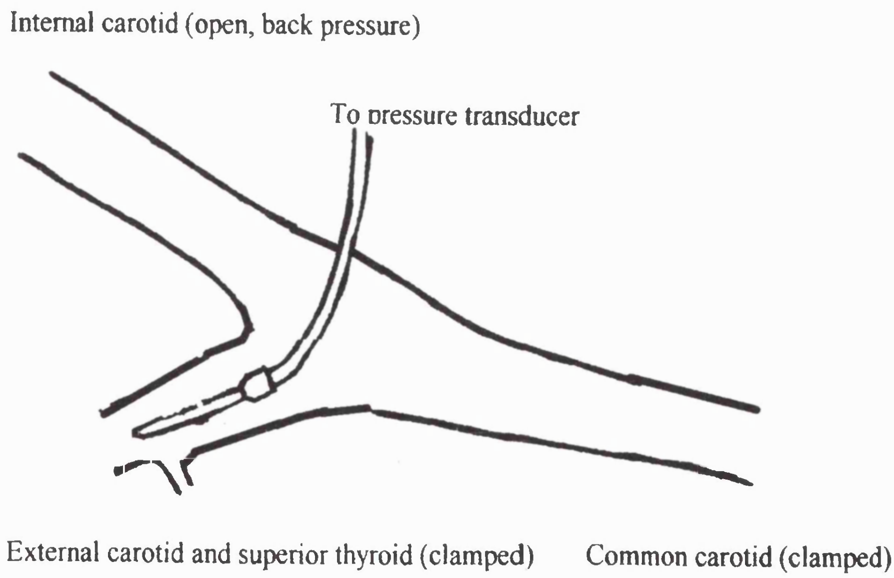


Fig 2.2b Diagram of stump pressure recording



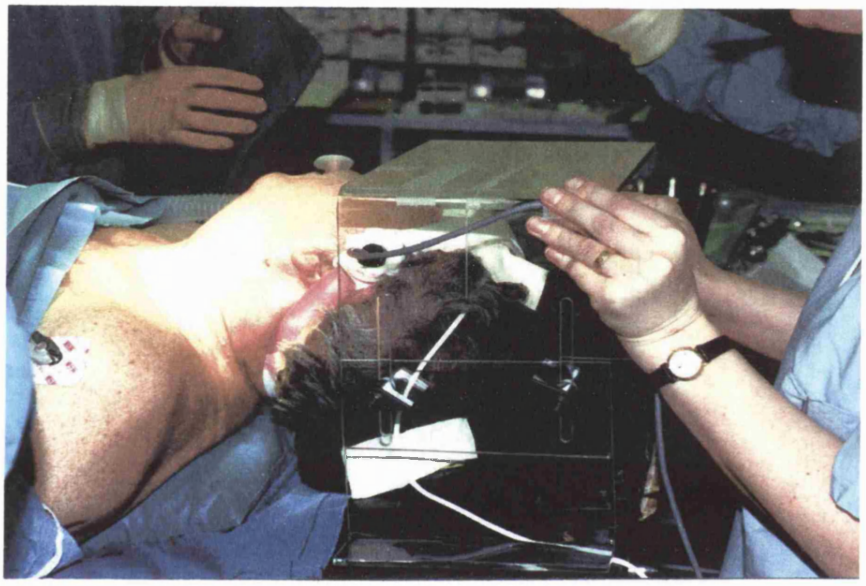
2.ix . Monitors 2: Blood Flow

Transcranial doppler has been used successfully to monitor patients for two decades since Aslid[96] and colleagues in 1982 developed a low frequency, pulse wave ultrasound beam which was capable of penetrating the cranium unlike conventional ultrasound. The new technology utilised natural "windows" in the skull where the bone is relatively thin or there is a gap for transmission of a signal. The usual site for insonation of the middle cerebral artery (MCA) with a 2MHz probe being via the thin temporal bone. The other sites are the transorbital route which insonates the carotid siphon and the suboccipital window which insonates the basilar artery.

Pre operatively the patient is assessed in the vascular laboratory to ensure they have a temporal window, which is absent in 15% of patients[97]. At surgery the probe can be placed either before or after induction of anaesthesia but once in position it requires protection by a head - box[98] or else it will tend to be dislodged by the surgeon or anaesthetist (fig 2.3).

Modern dopplers have the ability to focus the beam to different depths, allowing optimisation of the signal quality in individual patients. The information received is of blood flow velocity and not blood volume, which is displayed in two modalities - audio and visual. Usually three separate figures are displayed; the peak systolic velocity (PSV), the mean velocity (MV) and pulsatility index (PI). The audio trace is continuous and allows the technician to fix the TCD probe in the position of maximum good quality signal. It also allows the operating surgeon to make a judgement of the change in flow velocity during surgery without the need to look away from the surgical field, to hear emboli if/when they occur and alter surgical technique accordingly and lastly to have an audio assessment of shunt patency. The visual trace also represents flow but additionally shows whether the flow is forward or reverse in direction, with reverse flow being an abnormal situation associated with decreased flow in another segment of the circle of Willis. The visual trace has the ability to (currently retrospectively) differentiate between particulate and non - particulate emboli which have been proven to be associated with poor outcome when occurring in large numbers either per - operatively or in the first few hours post operatively.

Fig 2.3 Head box for protection of TCD probe



Ideally a technician should be present in theatres as adjustments are often required to the probe to maintain a good quality signal throughout the time span of the operation, with obvious cost and staffing implications. Unfortunately most hospitals in the UK do not have a large vascular studies unit and so the probe is often fixed in situ and protected at the start of the case and then left unattended.

A decrease in flow rate of 40 - 60% has been taken as being significant and indicative of the need to insert a shunt[(99)] however Gianoni et al[(100)] monitored over 100 patients under locoregional anaesthesia and found that this was not the case. Our series also had similar figures[(101)] leading to the conclusion that the current TCD criteria over estimate the need for shunts. Based on the combined data of the Giannoni and ourselves a more restricted set of criteria would appear to be a loss of TCD signal or flow < 10cm/sec.

As already mentioned, shunt patency and function is readily measurable by TCD. Occlusion will cause reduction in flow and decrease in the audio signal which should be noted as soon as it occurs. Malfunction with either entrapment of air by a Venturi effect or focus for clot formation will cause emboli which cause high intensity "chirps and beeps" to be heard and change in the spectral signal to be seen on the visual display. In the presence of either of these the shunt can be changed or repositioned.

The relationship of embolic load to outcome has been established in recent years[(102 - 108)] with increase in pre operative, per operative and post operative being associated with poor outcome.
A large number of emboli, which must be particulate since the arterial system is closed, heard in the pre operative phase is an indication for urgent surgery in the presence of a carotid stenosis or formal anticoagulation if of a non arterial source (AF, cardiac valvular disease etc). As mentioned above, emboli heard during surgery should alert the surgeon of the need to adjust surgical technique. Emboli heard in the post operative phase are more of a dilemma however; should re operation and exploration of the anastomosis occur, or should the patient be treated with anticoagulation. Much of the work on this subject has come from Leicester[(102 - 104, 107, 108)] where they have demonstrated that significant post

operative embolisation will occur within three hours of surgery and that an embolic load of $\geq$ 25 emboli per 10 minute period should be treated by an infusion of Dextran 40, commencing at a rate of 20ml/hr. If emboli continued to be detected their protocol is to increase the rate by 5ml/hr every 10 minutes to a maximum of 40ml/hr. Once the Dextran infusion is stabilised they leave it running for 12 hours. In their most recent series of 192 patients studied prospectively, none required surgical intervention in the post operative phase with the use of this protocol.

Surprisingly, eversion endarterectomy also appears to cause less post operative embolisation than standard endarterectomy[105]. In this study the number of emboli recorded was similar pre – operatively, during dissection and at clamp release, but was significantly different at cross clamp application and during 45 minutes of post – operative monitoring with the eversion technique being associated with lower counts. Although of interest this did not translate into a different complication profile with 2 patients in each group having neurological symptoms post – operatively and so it would seem unlikely that a change of operating technique will markedly effect outcome.

Transcranial Doppler may also be able to predict those who are at risk of a hyper – perfusion syndrome post endarterectomy[109 - 111]. It would appear that those who have a low perfusion pressure due to their carotid stenosis are vulnerable to hyper perfusion and intracranial haemorrhage, but if a marked rise in TCD signal is detected the potential injury can be minimized by controlling blood pressure.

2.x Monitors 3: Electrical Activity

Electroencephalography (EEG) reflects the electrical activity of the cerebral cortex as measured from the scalp by either a standard 16 lead bilateral monitoring or modified 8 lead ipsilateral monitor[112 - 114]. Analysis of the trace during carotid surgery focuses upon the frequency, amplitude and distribution of the waveforms[112]. An awake adult with eye closed has predominant beta (>13Hz) rhythm anteriorly and alpha (8 - 12 Hz) rhythm posteriorly. After induction of general anaesthesia several drug dependant changes occur. The predominant change is a generalised spread of fast activity (beta) which is superimposed on an admixture of theta (4 - 7 Hz) and delta (0 - 3 Hz) rhythms. Intraoperatively the EEG may be altered by a number of metabolic factors: electrolyte abnormalities, oxygen saturation, arterial CO_2 and temperature, however these are usually systemically constant under general anaesthesia.

For the EEG to be a useful intraoperative tool it needs to be applied to the awake patient prior to the induction of anaesthesia in order to identify any pre - operative abnormalities in rhythm, which have been reported in 9.8 - 29% of patients undergoing endarterectomy[112 – 114].

The majority of clamp related changes occur within one minute of clamp application, and vary from subtle increase in slower frequency activity and mild loss of beta activity to complete loss of all detectable electrical activity. The brain requires a flow of 18ml/100g tissue/min[113] to sustain a normal EEG These changes are usually ipsilateral to the side of the occlusion, although bilateral changes can occur in those with severely compromised collateral circulation. The changes seen can be classified as major or minor. Major changes (seen in 15 - 20% of patients) are defined by a minimum of 75% attenuation of all activity and/or a twofold or greater increase in delta activity in the range <1Hz[112]. The differentiation between groups is slightly arbitrary since patient with "minor" change can have subsequent neurological deficit , and so some would state that all changes are significant[116].

Shunt placement resolves EEG changes in 2 to 7 minutes, although longer times may be required. Approximately 1% develop persistent focal changes that are associated with immediate post operative neurological deficit[116].

Despite this several authors have not found EEG to be at all useful as an intra operative monitor, since it does not always demonstrate ischaemia which causes neurological sequelae[117].

To differentiate those changes secondary to emboli as opposed to haemodynamic insufficiency one needs to have a second measure of cerebral blood flow such as Xenon clearance, since in trials where EEG and TCD are used as monitoring the EEG did not always change with a run of emboli which caused a post operative neurological deficit[118].

In summary EEG has not gained universal popularity since it does not always demonstrate ischaemia, often misses significant emboli and requires highly skilled (and expensive) personnel to run and interpret the traces.

Somatosensory evoked potentials (SSEP) are episodes of cerebral activity caused by artificial stimulation of the periphery. The principle behind this technique is that in the normally functioning well oxygenated brain stimulation of the periphery will result in characteristic reproducible neuronal discharge with a fixed time of delay from stimulation to reaction. If the functional ability is obtunded by ischaemia there will be a delay and this would indicate the need for restorative maneovures. To achieve this needle electrodes are placed into the contralateral wrist in order to stimulate the median nerve, and scalp electrodes are placed over the somatosensory cortex with a further reference electrode placed over the frontal region. Prior to the administration of muscle relaxants the wrist electrical stimulus is set at a level to cause twitching. In the case of a carotid endarterectomy this system is set up bilaterally to allow comparison of the operated and "control" hemispheres[(119)].
During the procedure baseline SSEP are recorded sequentially by alternate median nerve stimulation prior to application of cross clamps. During cross clamping continuous recordings of the hemisphere under study are made, and contralateral recordings performed for comparison whenever any change occurs. The traces thus obtained are analysed for changes in amplitude and for prolongation in conduction time, with amplitude changes being the earlier sign of ischaemia. An amplitude change of 49% is considered an indication to shunt[(120)]. Most published work has demonstrated sensitivities and specifities in the range 60 - 100%[(121 - 125)], although the changes seen have the same disadvantage as those shown on EEG, i.e. the deterioration only occurs after the hypoxic insult has occurred, with conflicting views being held on its value as a monitor[(123 - 124)].
The other major disadvantages of this technique is the need for a skilled technician to be available throughout the procedure to interpret the traces as they are produced, the intermittent nature of the monitoring which requires 1 minute of stimulation and its use is limited to the central and parietal regions of the brain[(120)].

These combination of factors have caused SSEP, like EEG, to not be universally accepted as a monitor.

2.xi Monitors 4: Tissue Oxygenation

Conjuctival oxygen saturation[126] is again an attractive method of assessing the cerebral circulation since it involves a readily accessible region of the body and is non - invasive. Unfortunately the changes seen are acutely sensitive to any change in carbon dioxide tension causing vasoconstriction. In addition the changes in conjunctival saturation seen at carotid cross clamping do not correlate with other monitors and the inter - individual variation means that it is not possible to define a "significant" level of desaturation. This has led to the abandonment of the technique as a clinical monitor.

Jugular venous saturation (JVS) has been used as a "gold standard" in research projects looking at the cerebral circulation and oxygenation. The catheter can be inserted by a percutaneous pre - operative technique, or as an open procedure once the carotid bifurcation has been displayed. Once the catheter is in the vein it is passed cephalad until it abutts against the jugular venous bulb, and is then sutured in place.

The primary reason for its use in research as opposed to clinical settings is twofold; firstly the catheters are single use only and cost approximately £100, thereby adding significantly to the costs of the procedure. Secondly JVS gives information regarding the oxygenation of the brain as a whole (including a component from the non operated hemisphere) rather than any particular "at risk" area and so it is quite possible for venous saturation to remain fairly steady in the presence of a significant focal desaturation. This combination of factors means that JVS is not suitable as a solo intra - operative monitor.

In addition those (our group included) who use JVS to measure a dynamic intra - operative situation have found that if the sensor becomes adherent to the venous wall of the jugular bulb that the results forthcoming are unreliable and swing from one extreme of the range to the other[127].

In the research setting these problems have limited impact since the JVS readings are not being used to make clinical decisions but rather are used as a comparative guide for the other monitoring systems.

In conclusion JVS is a useful reference for research purposes when looking at tissue oxygenation, but is not suitable as a solo monitor in carotid surgery.

Near - infrared spectroscopy is described in the following chapter.

2.xii Monitors 5: Research tools, non - clinical

Several other methods exist of assessing the cerebral blood flow using either radioisotope scans or radiological investigations. These are however strictly "laboratory" investigations since they are cumbersome, expensive, involve ionising radiation and a great deal of technical support. None of them shows promise as a clinical tool for these reasons, but have occasional value in the research setting.
Single positron emission tomography (SPECT) is a modified CT scan of the brain and yields information regarding the regional blood flow in the brain. Pre operative scans in those with previous cerebral infarcts may demonstrate those with poor collateral supply and areas "at risk" during carotid cross clamping[128 - 130]. However since it is not a portable technique and so cannot assist during surgery, its value is limited.

Xenon clearance involves giving repeated intra arterial injections of ^{133}Xe per operatively and using a detector over the temporal region to count the emitted radio active particles and then calculate regional blood flow on a washout basis[128]. This technique has the logistic disadvantages already mentioned, but is a very accurate assessor of blood flow.
Unfortunately investigators have found that it is impossible to predict the critical threshold for symptoms in patients under GA, and so Xenon clearance is at best a guide. Also, in one trial those with the highest blood flows had the worst outcome, with the authors postulating that this group probably suffered embolic events or had a small watershed area which became ischaemic[130].
Technecium labelled red cells an be used in a similar way, with the same disadvantages[128].

2.xiii Monitors 6: Intervention Threshold

Monitor	Criteria
Local anaesthesia	Change in neurology
Stump pressure	<50mmHg
EEG	Change in waveform
SSEP	Amplitude change/prolongation
TCD	Flow change > 40%
NIRS	>10% fall*

*verbal communication, Prof McCollum, Manchester

The above thresholds are commonly used as the accepted limits of change which can be safely seen without a neurological deterioration in patients undergoing carotid endarterectomy. There is some controversy since these were not produced by assessing large groups under loco regional anaesthesia and so have been formulated either by "best guess" or by comparing intra operative change with outcome in those under general anaesthesia. Additionally some criteria have been deduced by simultaneously monitoring patients with a new and an established system, but since no system is perfect there is an absence of a reference from which to calibrate. Overall these criteria (other than level of consciousness in locoregional anaesthesia) are at best a guide, but at worst can mislead the operator.

Conclusion

Carotid cross clamping potentially can cause cerebral hypoperfusion and neurological insult. No monitor can accurately cerebral hypoperfusion, ischaemia or dysfunction although transcranial Doppler can detect emboli, is "real - time", can demonstrate problems with a shunt and at clamp release will not change if there is a distal occlusion.

Increasingly locoregional anaesthesia is being used which allows awake neurological testing throughout the procedure and especially at times of cross clamping. This has the advantage of keeping shunt rates to a minimum and also allows the surgeon to assess whether the shunt is producing satisfactory perfusion. At present no recommendation regarding method of anaesthesia can be made, although the GALA Study is ongoing and may answer this conclusively.

With the current data available no monitor, anaesthetic technique or shunting protocol appears to be superior, but whatever technique is used the surgeon needs to audit their figures and modify practice as the evidence base changes.

Chapter 3 The History of Near - Infrared Spectroscopy

Biochemical Background

The process by which the cells of the body produce energy is called respiration, and can occur in two contrasting environments - aerobic where there is an adequate supply of oxygen, and anaerobic where there is an inadequate supply of oxygen. The former is a highly energy efficient process whereas the latter is both highly inefficient of energy and productive of toxic substrates. Not surprisingly aerobic metabolism is sustainable and the normal state of affairs whereas anaerobic metabolism is short lived and non sustainable.

Glycolysis

The blood stream of a healthy human contains multiple substances, but the two most important for successful cell metabolism are oxygen and glucose. Oxygen enters the cell by a process of diffusion from the high tension in the capillary bed to the low tension in the cell, glucose is taken up by an active process by an intra cellular membrane pump. Once inside the cell the glucose is metabolised in the cell cytosol by a series of enzymic reactions, the purpose of which is to produce pyruvate (see fig. 3.1a) and additionally 2 molecules of adenosine triphosphate (ATP) per molecule of glucose. Once pyruvate is produced the cytosol no longer has a role to play, with all further biochemical reactions and energy production taking place in the mitochondria.

Acetyl CoA formation and the Krebs cycle

The first step (fig. 3.1b) is the oxidative carboxylation of pyruvate to form acetyl coenzyme A (acetyl CoA). This initial step takes place in the mitochondrial matrix, as do all subsequent energy releasing reactions. The acetyl CoA combines with oxaloacetate to tricarboxylic acid (citrate) to initiate the Krebs Cycle (see fig. 3.1c), the overall effect of which is:

$$\text{Acetyl CoA} + 3NAD^{+} + FAD + GDP + P_i + 2H_2O =$$
$$2CO_2 + 3NADH + FADH_2 + GTP + 2H^{+} + CoA$$

The importance of this cycle is that it produces NADH and $FADH_2$ which are oxidized by the electron transfer chain (see below) with the production of 2.5 ATP molecules per NADH and 1.5 ATP molecules per $FADH_2$. In addition one high energy phosphate bond is formed per acetyl CoA entering the Krebs cycle, but a further nine are generated by NADH and $FADH_2$ in the electron transfer chain. Despite the absence of oxygen from any direct part of the Krebs cycle, the process is strictly aerobic because the NAD^+ and FAD that are required to sustain it can only be regenerated in the mitochondrion by the transfer of electrons to molecular oxygen.

Oxidative phosphorylation

NADH and $FADH_2$ both contain a pair of electrons of high transfer potential which, when donated to molecular oxygen, liberate a large amount of free energy which can be used to generate ATP by a process known as oxidative phosphorylation. It is a highly efficient process and generates 26 of the 30 ATP molecules created by the conversion of glucose to carbon dioxide and water.

Oxidative phosporylation occurs in the mitochondria; electrons flowing from NADH or $FADH_2$ to O_2 through three protein complexes located in the inner membrane of mitochondria leads to pumping of protons out of the mitochondrial matrix, resulting in a pH gradient and a transmembrane electric potential. ATP is generated when protons flow back to the mitochondrial matrix through an enzyme complex. NADH and $FADH_2$ have initially different pathways with NADH donating more high potential electrons thus creating additional ATP. NADH enters the chain at a large proton pump known as NADH - Q reductase (first protein pump) which transfers two high energy electrons to flavin mononucleotide, which in turn transfers them to iron - sulphur clusters. $FADH_2$ enters the chain at this point by directly transferring its electrons without the use of a protein pump. For both NADH and $FADH_2$ the pathway is now common. Electrons from the iron - sulphur complexes are shuttled to coenzyme Q and then transferred to cytochrome c in the presence of the catalyst cytochrome reductase (second protein pump). *A cytochrome is an electron transferring protein that contains a haem prosthetic group. They have the ability to absorb light and the different wavelengths at which they do so allows them to be discriminated from each other.* The electrons of cytochrome c are then transferred to molecular oxygen in the presence of cytochrome oxidase (third protein pump). This third pump contains both iron and copper ions and has subunits known as cytochrome a and a3.

Fig 3.1a. Glycolytic pathway

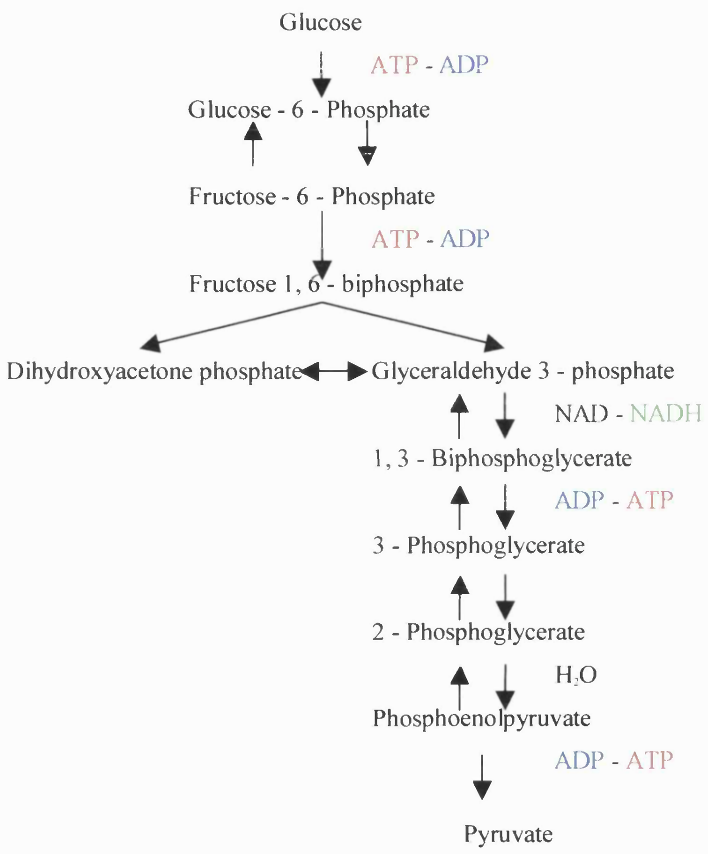
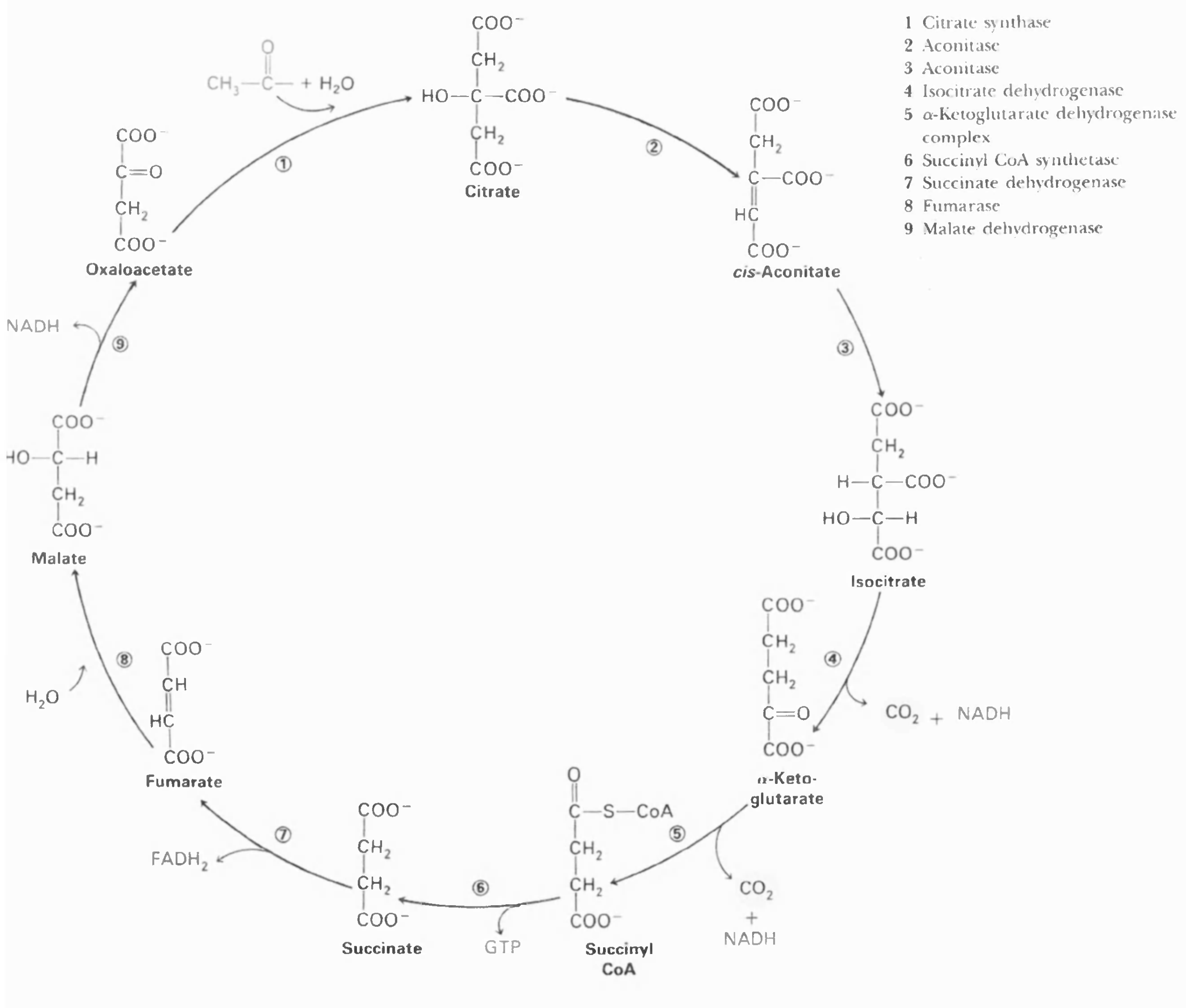


Fig 3.1b and c. Oxidative carboxylation of Pyruvate and Kreb's cycle

Pyruvate + CoA + NAD = Acetyl CoA + CO2 + NADH



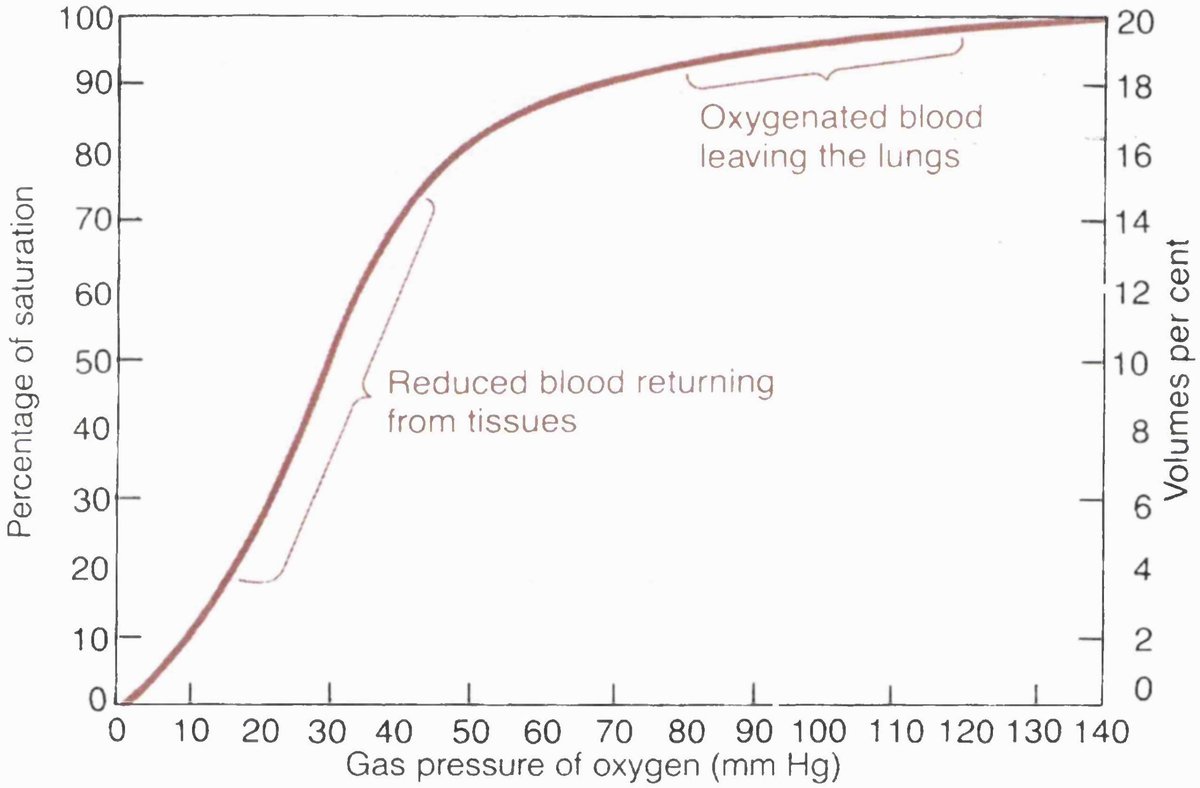
Haemoglobin

Haemoglobin is the specialised oxygen transport protein contained in red blood cells. Each molecule consists of two pairs of polypeptide chains held together by non covalent attractions, with each chain containing a haem (iron containing) group and single oxygen binding site. In addition to O_2, haemoglobin is able to bind and transport CO_2 and H^+. It is defined as an allosteric protein due to the complex nature of its structure which means that H^+, $CO_2$and organic phosphates binding to sites remote to the O_2 binding site can have a profound effect on O_2 uptake and release.

A summary of its abilities are:
The binding of O_2 enhances the binding of further O_2.
The presence of H^+ and CO_2 promote the release of O_2
2, 3 Biphosphoglycerate (BPG) decreases the affinity of haemoglobin for O_2

The effect of these combined properties is to create a carrier molecule which is capable of picking up O_2 in an O_2 rich environment (such as the lungs) with the simultaneous dumping of CO_2, but then dumping O_2 and picking up CO_2 in an environment rich in H^+, CO_2 or BPG (such as active cells), see fig 3.2.

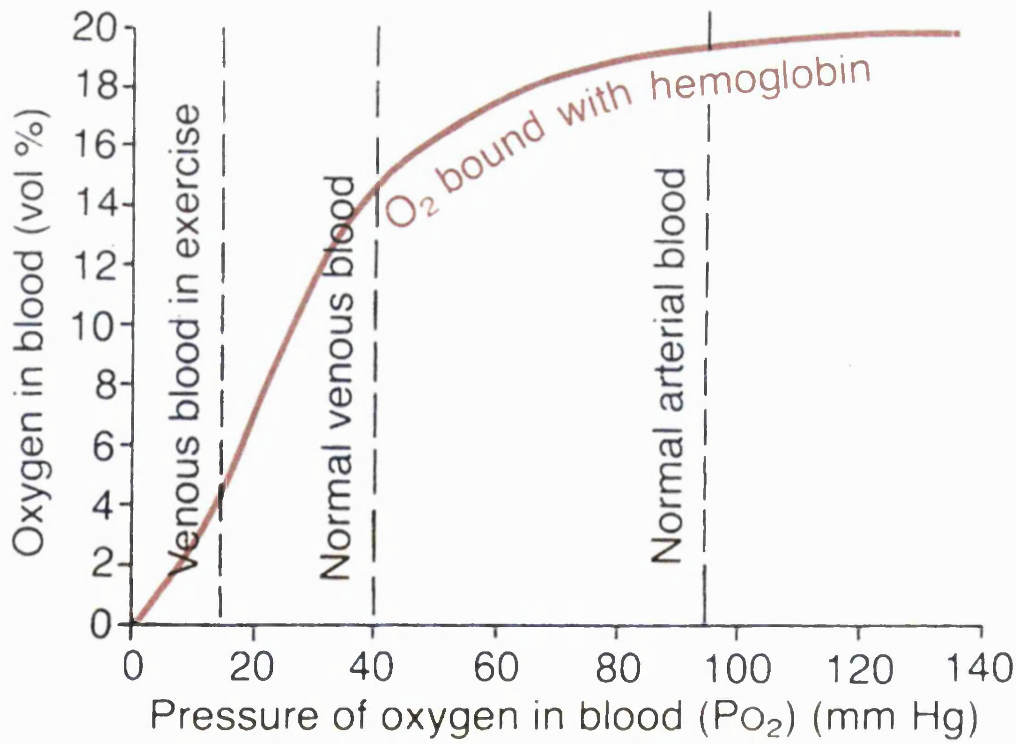
Fig 3.2. Oxygen dissociation curve



The change in O_2 content which occurs between the (high) arterial and (low) venous system can be seen clinically by the change in colour from bright red arterial to maroon venous blood.

The extraction of O_2 is not fixed, at extremes of exercise, or continued metabolism in the presence of a poor O_2 supply, the cells will extract more leading to a greater desaturation of haemoglobin (see fig 3.3).

Fig 3.3. Change in oxygen extraction with exercise



Organ oxygenation assessment

Clinical assessment of tissue oxygenation begins with visual inspection of colour, palpation for temperature and examination of pulses for presence and character. This basic examination can adequately assess peripheries for gross inadequacies but is less reliable for subtle changes and cannot assess internal organs. Indirect measures such as blood pressure and pulse rate do give some further guide but again will miss subtle degrees of impairment, are not as reliable in the presence of atherosclerosis and cannot exclude regional failure such as to the renal or cerebral bed.

Indirect cutaneous measurement of haemoglobin saturation has been performed for over fifty years, with Millikan[(132)] first describing the use of an ear probe in 1942. The basis for his device was that the cutaneous blood flow was predominantly arterial blood diverted to the skin to facilitate thermal regulation and as such was an indirect measure of the arterial oxygen tension. This device is no longer used since the development of the pulse oximeter[(133 - 135)] in the 1980's. This device selectively assesses the oxygen saturation of the pulsatile flow in the digit in order to reduce signal contamination by venous blood. The disadvantage of this device is that it does not function well in situations where the capillary bed of the digits is vasoconstricted, such as cold and shock. Additionally both the above devices are measures of global rather than regional saturation and so suffer from the same problems as clinical assessment.

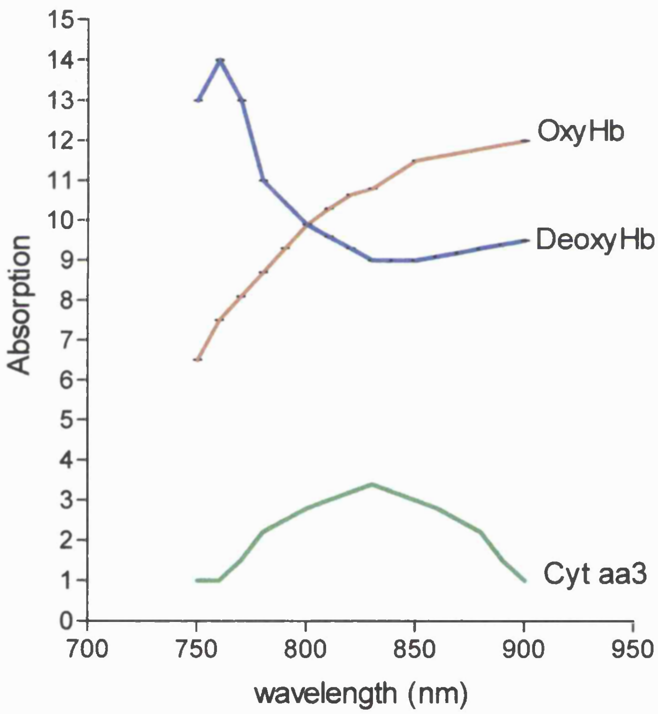
Direct measure of arterial oxygenation by the taking of arterial blood gases is an extremely accurate method of assessing pulmonary function and gaseous exchange but again does not give information about regional tissue oxygenation and can lead to a false sense of security.

In most circumstances regional oxygenation will mirror the global condition, or the regional deficiency will be clinically obvious (such as an acutely ischaemic limb) and will be the reason for medical intervention. The brain is a special case since inadequacy of tissue oxygenation results in an initial deterioration of mentation followed by a gradual descent into coma if remedial action is not taken. In patients who are initially conscious this should be noted and treated, but for those under general anaesthesia clinical assessment is impossible. Other indirect measures, such as evoked potentials and transcranial Doppler, have been discussed at length in the previous chapter. This problem with cerebral assessment has lead to a recognition of the need for a measure of regional cerebral oxygenation, but the physical barrier of the skull has made this extremely difficult.

Light absorbance and oxidation

Both cytochromes and haemoglobin have the ability to absorb light. The quantity of light of any given wavelength absorbed is dependant on the oxidation status of the molecule at that time and so absorption spectra can be produced, see fig 3.4 [136]. By the reverse process, analysis of the absorption of light of different wavelengths passed through tissues can determine the amount of cytochrome and haemoglobin contained therein and their oxidative status.

Fig 3.4. Absorption spectra of Haemoglobin and Cytochrome aa3



Near infrared light (700 - 1100nm) also has one additional property that makes it of great interest and importance, it is not absorbed by skin or bone to any great degree and so has the ability to pass through a biological field with any absorption being related to tissue oxidative status rather than the media itself.

Exploitation of this straight forward physical property has involved a great deal of research and time. Initial interest was directed at mitochondrial cytochrome because it is the catalyst in 90% of oxygen consumption, with haemoglobin being largely ignored or considered to be a troublesome contaminant. Before 1985 most experiments were performed using purified mitochondria in laboratory cuvettes from varying animal tissues to fully quantify the absorption spectra[137, 142] which provided the biophysical background necessary. These experiments proved that the spectra from different tissues, such as liver and kidney, were not the same, but that the changes with oxidation were. The conclusion from this was that some tissue dependant biological/optical interference was present but that the trend which could be measured was the same. It was also found that light of wavelength >1300nm is rapidly absorbed by water over a pathlength of a few millimetres, rendering it useless in normally hydrated tissue.

Spectroscopic studies on fresh human cadaveric brain tissue in the spectral range 200 - 900nm[143] have been performed where an area of frontal grey and frontal white matter were dissected free from thirteen normal brains at post mortem. Blood was removed from each sample prior to being optically tested, with one area of grey matter being tested before and after removal of the arachnoid whilst the other twelve were all tested with arachnoid (average thickness 0.25mm) removed. Meningeal tissue was tested separately. For all tissues the degree of transmission, reflectance and scattering was measured at 10nm intervals from 200 - 900nm. With increasing wavelength the degree of reflectance increased and the degree of absorption decreased for white matter, grey matter and meninges. This reached a plateau in the near - infrared range (700 - 900nm), but with peaks of absorption corresponding to haemoglobin indicating that despite the researchers best efforts some haemoglobin must have contaminated in the study tissues. The conclusion from this is that native brain tissue will not have any significant effect on the near - infrared light passing through it but the oxidative condition of the tissue haemoglobin will.

The second thrust of research was in the development of an emitter/detector array that could be used clinically on the intact skull. Initial experiments were performed by transmission i.e. the emitter and detector were placed on opposite sides of a rat skull and the degree of absorption recorded. It was realised that this would not be applicable to the adult human skull and a further set of experiments were performed on cats(144), but this time using a reflectance method where the emitter and detector are placed several centimetres apart but both on the frontal bone, with prior removal of hair. Having established the feasibility of reflectance, human studies began. Again the method of reflectance over the frontal bone was used, with a rubber cover being placed over the probe heads to exclude ambient light. During the course of these experiments the investigators found that the haemoglobin signal which could in vivo be removed by the use of algorithms could not be dealt with in the same way in vitro. However the changes of haemoglobin with oxidation were measurable and of clinical use. A four wavelength spectral analysis was found to derive enough data obviating the need to measure the entire range. Measurements were performed every 0.2 seconds, with updates displayed every 1 to 5 seconds. The information displayed was of cytochrome aa3, oxygenated haemoglobin and reduced haemoglobin; summation of the two haemoglobin figures allows calculation of the total haemoglobin in the tissues.

Main Investigators

1. Franz Jobsis

Franz Jobsis[144 - 147] of Duke University, North Carolina, career spans four decades and who's earlier work and paper of 1977 had stimulated interest in near infrared technology for real time interrogation of living tissues. He has published widely and has developed two monitoring systems, one for clinical use and one for experimental. The clinical monitor is known as a Niros - scope, standing for *n*ear - *i*nf*r*ared *o*xygen *s*ufficiency scope whilst the experimental is known as the OMNI monitor, standing for *o*xidative *m*etabolic *n*ear - *i*nfrared monitoring.

2. Britton Chance

Emeritus Professor of Biochemistry and Biophysics at the University of Pennsylvania School of Medicine, Britton Chance[137 – 141, 148 - 150] has been publishing on optical properties and spectroscopy for half a century. He has contributed greatly to both the basic science of isolated tissues and toward the extremely complex mathematics involved with interpretation of the signal detected when the system is used clinically. He has also developed his own system known as the RunMan.

3 David Delpy

David Delpy DSC[151 – 159] Medical Physicist at University College London, is a relative new comer when compared with the two gentleman above since he has only been working in the field since the 1980's. His main thrust of research has been to try and establish the unknown factors in the complex mathematical formulae (see below) which describe the journey of a photon of light through a scattering media. The reason that this is potentially of great importance is that if one can establish all the unknowns it is then possible to have quantitative rather than qualitative data. His work has been with Hamamatsu photo multipliers, dye lasers and streak cameras.

Quantitative vs Qualitative Data

Qualitative change requires baseline measurement of "normal" so that variation from this can be detected. Quantitative data has known normal values already so that any measurement can be compared with these to assess whether it is inside or outside the conventionally accepted range. Most medically used data is quantitative, ie. pulse rate, blood pressure, pulse oximetry, and as such is useful since it allows us to assess those who are unwell and compare their results with historical controls to determine the degree of functional derangement. For data to be quantitative there cannot be a large number of unknown variables which are patient dependant.

With near - infra red spectroscopy the signal received at the detector compared to the signal transmitted is not only dependant on the oxidative condition of the tissue under study but also on the distance travelled and quantity of tissue encountered. For this reason quantification has not yet been achieved and so a qualitative trace is displayed. For most situations where an assessment is being made on a patient this is adequate since a baseline is taken and change with therapeutic intervention can be assessed and remedialised if detrimental.

Beer Lambert Equation and Mathematical Basis

The basis for near - infrared technology is that there is a relationship between the quantity of light absorbed by a tissue and the tissue chromophore content. This relationship is described by the Beer Lambert equation;

Optical density = (acLB) + G (equation 1)

a = absorption coefficient of chromophore

c = concentration of chromophore

L = pathlength of light through the tissues

B = Pathlength factor, taking into account the property of the tissue to scatter light

G = Tissue geometry related factor

If L, B and G remain constant during a study then the change in chromophore concentration will be directly proportional to the change in optical density;

$\Delta c = \Delta OD/aLB$ (equation 2)

Optical density can also be calculated from the logarithmic relationship of the ratios of incident and transmitted light;

$OD = \log Io/I$ (equation 3)

Io = incident light

I = transmitted light

If all factors other than tissue chromophore concentration are maintained constant then by combining equations 2 and 3 we see that changes in the ratio of incident and transmitted light will be proportional to changes in tissue chromophore concentration;

$\Delta c = \Delta OD = \Delta \log Io/I$ (equation 4)

This simple approach is unfortunately not entirely valid since further study demonstrated that the path length is not the distance between the emitter and detector array but the actual distance in the tissue that the photons of light travel which is not constant throughout a study period due to the changes in chromophore concentration and light scattering. This distance can be measured by the use of a pulse laser using the equation;

$L = ct/n$ (equation 5)

c = velocity of light

t = time taken

n = average refractive index of tissue

Combination of equation 1 and equation 3 gives:

$OD = \text{Log } Io/I = (acLB) + G$

replacing L as per equation 5:

$OD = \text{Log } Io/I = (ac[ct/n]B) + G$

In the above equation c (speed of light) is a known constant as are n (refractive index of tissue), a (absorption coefficient of chromophore) and B (pathlength factor). One can measure Io, I and t and since tissue geometry (G) will not change intra - operatively the only variable should be the changing concentration of chromophore in the tissue.

In the presence of a fixed light emission system, change in tissue chromophore concentration will be proportional to received light and the time of flight through the tissues (the pathlength), both of which are measurable.

Summary

Human metabolism causes changes in cellular components which contain haem groups and are known as chromophores. These chromophores absorb light at wavelengths dependant on their oxidative status and by applying a modified Beer Lambert equation one can calculate their changes with time.

Chapter 4 Background of Thesis

Introduction

As has been noted in the previous chapters there is an ongoing and large demand for carotid surgery which even in the best of hands carries with it the attendant risk of neurological injury. These injuries can be divided into peripheral nerve injury which is usually as a result of iatrogenic trauma during dissection and central nervous injury related to interruption of the cerebral blood supply. Some of these events will be caused by embolisation whilst others will be a result of cerebral hypoperfusion resulting in hypoxia. Embolic events can be reduced by meticulous surgical technique and the judicious use of anticoagulation. Hypoperfusion and hypoxia is potentially reversible by release of a clamp or insertion of a shunt.

Procedures being performed under locoregional anaesthesia have the advantage of allowing the operating surgeon and anaesthetist to continually assess the patient and only perform manoeuvres which are clinically indicated, which could lead to the recommendation that all carotid surgery should be performed under local anaesthesia. Unfortunately not all patients are willing to accept an awake procedure and those who have disease which extends up toward the angle of the jaw may well find the retraction needed to access the distal extent of the disease too painful to tolerate. There will also be occasional patients with recurrent carotid disease which is much more time consuming to dissect and a small number who have a movement disorder such that anaesthesia is required to render them still. The above are just some of the situations in which a general anaesthetic will have to be employed.

At carotid cross clamping the surgeon can then either be a non – shunter, a selective shunter or a mandatory shunter. The former avoids potential shunt injury, but does expose the 15% of patients who are shunt dependant to a (potentially long) period of cerebral ischaemia. The latter approach is safe from the perspective of hypoxia but does not remove the risk of embolisation and adds iatrogenic shunt induced injury to the complication profile of the procedure. Selective shunting would seem to be a logical approach, but requires some monitor to assist the surgeon in the decision process.

Requirement

The ideal monitor would be accurate, user friendly and reliable. It would assess the end organ (the brain) directly and measure cerebral oxygenation in real time. Secondary considerations would be the ability to detect embolisation and warn of shunt dysfuction. Changes in cerebral vasoactivity in response to clamping or pharmacological agents should only effect the recording if they result in an alteration in cerebral oxygenation. Movement during operation should have little or no effect on the quality of the monitoring.

Near – infrared spectroscope (Critikon 2020)

On first inspection the Critikon 20202 Near infrared spectroscope would appear to be ideal since it has the attractive property of measuring the oxygenation of the end organ and has been claimed by its manufacturer to be accurate, reliable and easy to use. Its method of recording should reduce the potential for other factors, such as anaesthetic agents, to confuse the picture since changes in vessel vasoactivity should not influence the result. However at the outset of this thesis no data applicable to carotid surgery was available.

Hypothesis

The Critikon 2020 Near – infrared spectroscope will be an accurate and easy to use monitor of intra – operative cerebral oxygenation which will be able to predict the need for patients to require a carotid shunt at times of cross clamping and will detect changes in cerebral oxygenation in response to significant embolic load.

Experimental structure

Firstly, can the system detect changes in intracerebral haemoglobin concentration in a cadaveric model.

Secondly, which position on the skull gives the most reliable recording of change in cerebral oxygenation.

Thirdly, what degree of cerebral oxygenation change can be tolerated prior to cerebral dysfunction.

Lastly, is there a detectable change in cerebral oxygenation with embolic load.

Design

1. System verification

To address the first question, in conjunction with the physicists from Johnson and Johnson Medical, we used a human cadaveric model to assess whether the system could in reality penetrate the human cranium and measure changes in intracerebral concentration of haemoglobin both reliably and reproducibly.

The stimulus for this was concern in the literature that near – infrared light was not penetrating the adult human skull and was merely recording changes in scalp oxygenation. The previous work by Johnson and Johnson had involved mathematical modelling, plastic "phantom" heads and porcine skulls, all of which suffer from the problem that they do not directly translate to the human situation. This is especially true in the case of the pig where the skull has a completely different geometry, a smaller brain and the bone being both thicker and softer. This led to the need to formally prove that the system did penetrate the harder human cranium and was capable of recording change in Haemoglobin concentration with time.

A living human model has been used at the time of scalp flap and craniotomy during neurosurgical procedures, which has shown that the scalp signal plays only a limited role in the overall near – infrared trace. Whilst of significant interest this work suffers from the problem that the amount of blood in the brain at the time of recording was not known and the investigators had no control over how this changed with time. This meant that the system could not be calibrated to allow quantification and all changes seen were relational rather than absolute.

This drove us to use a cadaveric post mortem model where the brain has been removed since it allowed us to repeat the same experiment to demonstrate reproducibility, commencing with a blood free field as a "zero" point from which to increase. Use of cadavers allowed us to maintain conditions across subjects and thus reduce errors.

The major advantage of this model is that the skull geometry and constitution are human. The disadvantages are that the temperature is far below that of a living person and the superficial tissues do not have a blood supply, but there is no avoiding these conditions due to the nature of post mortem gravitational shift of blood and safe storage of a dead body.

An alternative to post mortem subjects would be cadavers in dissecting room, which are at a slightly higher temperature but have the major disadvantage of being preserved in formalin which causes the blood remaining in the tissues to thrombose, a potential source of interference.
Our model therefore seemed to be both simple and practical, with the additional advantage of being easily reproducible in another centre.

2. *Probe position*

Having established that the system could record changes one sought to discover the optimum probe position for reliable and accurate recording. In the neonate a bi – temporal transmission probe array has been used to great effect, but this is only applicable to the very thin neonatal skull and to the special circumstances surrounding sick babies in whom bilateral monitoring is warranted. In the adult undergoing carotid surgery the requirement is for measurement of one hemisphere or region of that hemisphere.

Other investigators have used two sites – the temporal and the frontal - with various advantages claimed for both. The proponents of the temporal stating that it was the region of the brain perfused by the middle cerebral artery and as such a "truer" reflection of carotid supply, whilst those who used the frontal cite ease of application and probe maintenance as its main advantage. Unfortunately no – one had compared the two in the same patient by simultaneous monitoring and so there was uncertainty as to which, if either, was superior and should be promoted.

By applying probes at both sites in the same patient during carotid surgery we intended to establish which site gave a more accurate picture of change in cerebral oxygenation with secondary endpoints being how commonly complete probe failure, poor quality recording and premature probe displacement occurred. Initial work was with the ancillary equipment supplied by the manufacturer, consisting of headbands and self adhesive probe covers. The development of modifications of this equipment and methods to reduce failure rates was an ongoing part of the project.

3. Cerebral dysfunction

Measuring changes with time is of intellectual interest, but unless one knows at what level to intervene by a therapeutic manoeuvre then one may as well not bothering in the first place. At the time of commencement of this thesis there was no known acceptable level of desaturation in the adult. Other investigators had compared near infrared systems with more established monitors such as transcranial Doppler and had correlated the recordings to try and identify a point related to cerebral dysfunction. This work suffers from the fundamental flaw that there is no perfect monitor with which to compare and so a large error is introduced into all these studies.

We therefore chose to use patients level of consciousness and ability to perform tasks as the sole indicator of cerebral function, with evidence of deterioration being taken as a significant desaturation.

Two points of ipsilateral monitoring were employed initially to identify which region was more significantly effected. Having established this, bilateral monitoring was commenced to assess whether there was any kind of "steal" phenomena between the two cerebral hemispheres at times of surgery induced hypoxia.

4. Embolic load

The presumed mechanism by which emboli cause damage to the brain relates to their lodging in the intracerebral vessels, causing obstruction to flow and consequently distal ischaemia. At surgery a variable amount of emboli which can be detected by transcranial Doppler are caused by the surgeon, with likelihood of neurological injury related to the magnitude of the embolic load.

Monitoring with simultaneous near – infrared spectroscopy and transcranial Doppler should allow retrospective analysis of the recorded audio trace compared with the spectroscopic recording to identify any change in cerebral oxygenation associated with embolic showers.

Chapter 5 Near - infrared spectrometer technical data

All experiments conducted in this thesis have been conducted with the Critikon 2020 Cerebral RedOx monitor (Johnson and Johnson Medical Ltd). This model uses four near - infrared laser diodes operating at 777, 819, 871 and 909 nm which are sequentially pulsed at a repetition rate of approximately 1.8 kHz. The duration of each laser pulse is 100 nsecs with a peak power output of 10 W. Each laser wavelength is maintained by controlling the laser diode temperature using a Peltier device.

The patient probe (see fig. 5.1a and b) consists of three active components - a photoemittor, two photodetector arrays and an light emitting diode (LED). These are encased in a shaped rubber mounting which conforms to the patients skull. The two photodetection arrays use high sensitivity photodiodes located 13 mm and 45 mm from the emitter window (see fig 5.2). For each channel the photodetected signals are amplified, integrated and then passed to a sample and hold for analogue to digital conversion using a 16 bit analogue - to - digital converter. Optical coupling with the tissue under question is assessed using the LED. If this demonstrates an inadequate couple it will cause "Poor signal" to be displayed on the monitor, allowing improved placement to occur.

The two arrays of detectors are designed so that the short distance pathway (13mm) samples the superficial tissues only, whilst the long (45mm) samples both the superficial and deep tissues. Subtraction of the signals is performed with the intention of removing superficial (scalp) contamination from the overall trace and leaving the user with a “pure” cerebral trace.

The probe should be placed on the subjects head; either on the forehead to assess the frontal area or, after a limited head shave, on the temporal region. Both an adhesive pad and a specialized head band are provided by the manufacturer to achieve this.

Fig. 5.1a Critikon 2020 probe

Fig. 5.1b. Critikon 2020 probe, cable and optical couple

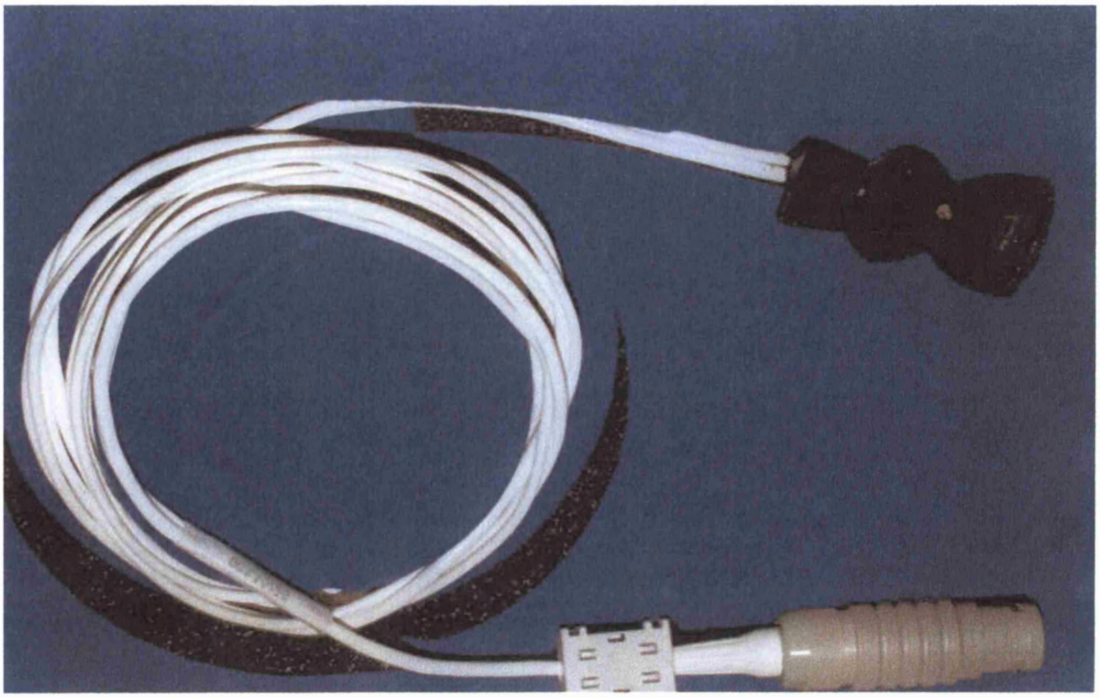
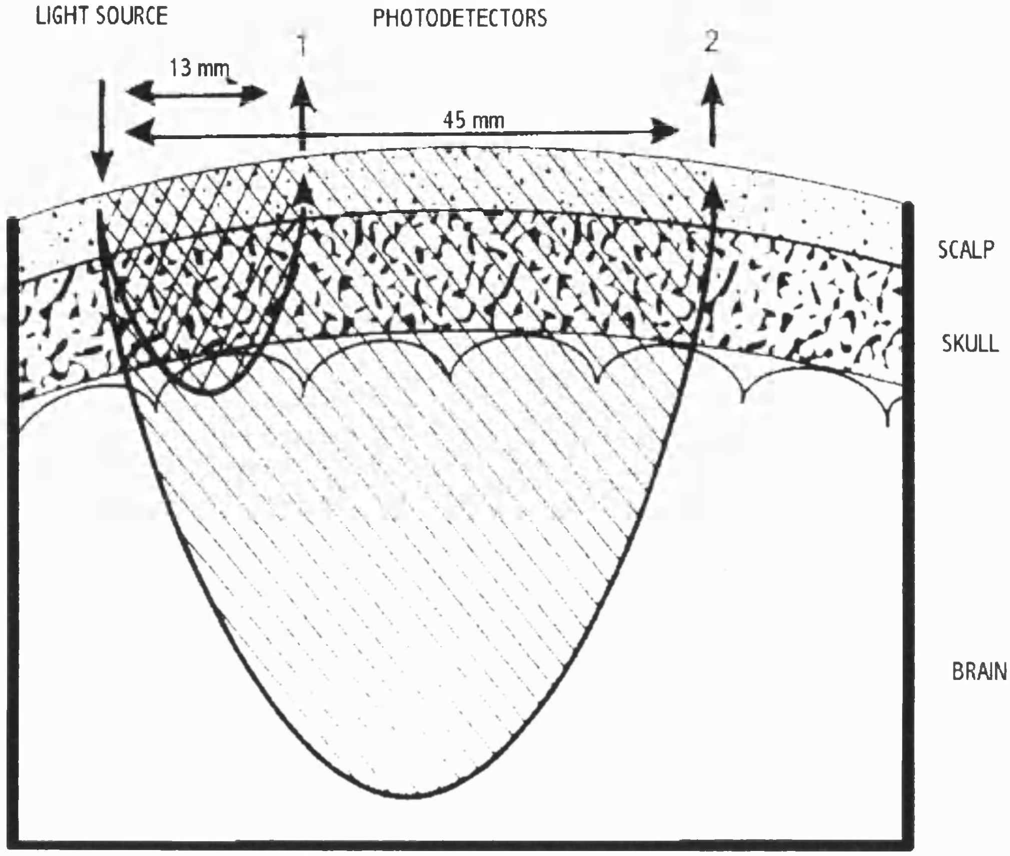
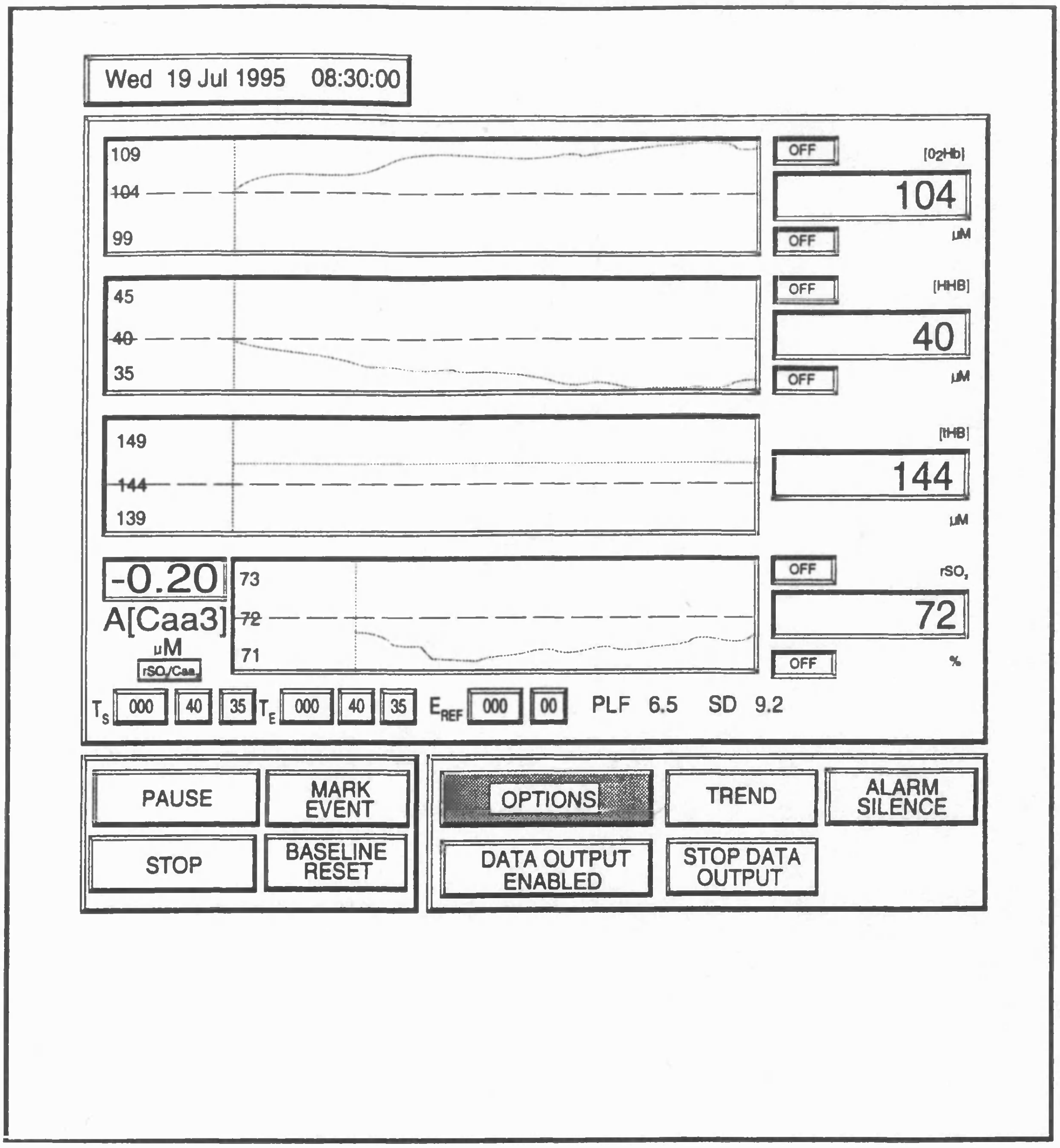


Fig 5.2 Effect of detector seperation distance on signal received



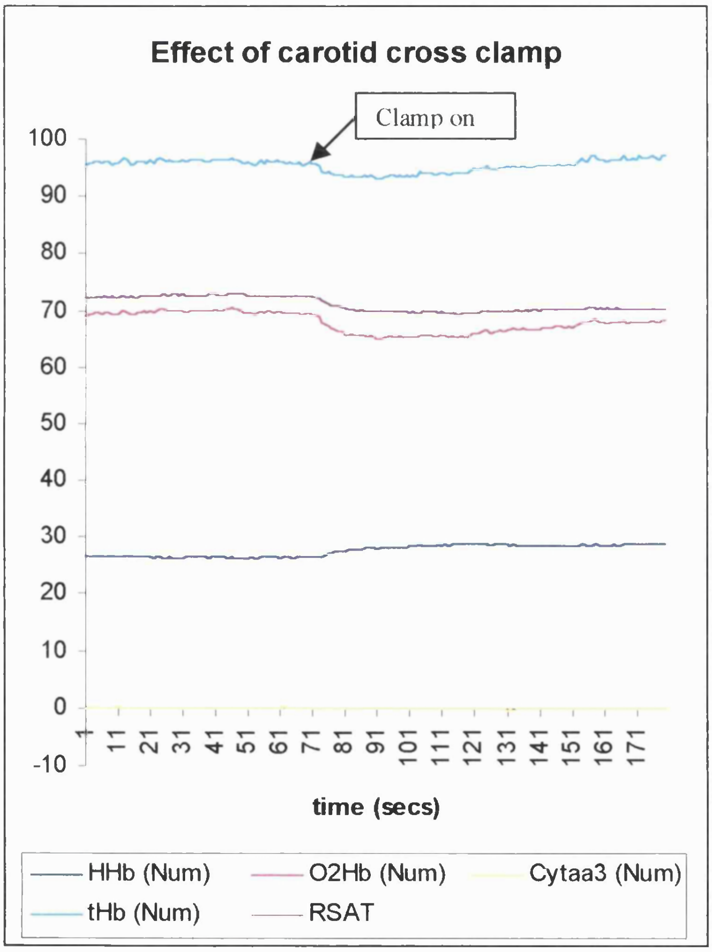
During data recording the screen display (see fig. 5.3) will show information on oxygenated haemoglobin (O2Hb), deoxygenated haemoglobin (HHb), total haemoglobin (tHb) and regional saturation (rSO2). The rSO2 trace can be exchanged for cytochrome aa3 (caa3), however the caa3 trace is not as useful an indicator of tissue oxygenation.

Fig. 5.3 Critikon 2020 display



Data produced is transferred via an RS232 port to computer, with a minimum requirement of a 386 processor to run the custom made Critikon Datalogger software. Once stored in a datalogger file the information can be reviewed (see fig. 5.4) and points of interest exported to spreadsheet for subsequent analysis and graph production. All analysis in this thesis was performed on Microsoft Works or Microsoft Excel.

Fig 5.4 Example of operative trace



Chapter 6 Experimental Verification of the System

Introduction

The monitoring equipment used for the collection of data in this thesis was a commercially available NIR system (Critikon 2020, Johnson and Johnson Medical). It had been developed by mathematical modelling, phantom head block studies, porcine cadaveric head studies, healthy volunteers using a scalp tourniquet, patients undergoing craniotomy and latterly by studying neurosurgical patients undergoing cerebral angiography by noting the fall in cerebral haemoglobin concentration associated with the displacement of blood by bolus injection of contrast media, which itself is not an absorber of NIR light[160 - 163].
These studies had shown that quality of cerebral signal improved with increasing separation distance from emitter to detector and led to the development of first the Critikon 2001 and then the Critikon 2020 systems.

Initial experience led the development physicists to believe that the system was capable of quantifying the value of haemoglobin in its oxidised and reduced forms. Quantification would enable the "normal" range of cerebral oxygenation to be established, which would be of particular use in assessing the efficacy of treatments in the setting of acute resuscitation or in monitoring patients with multi – organ dysfunction in intensive care. With increasing use of the system doubts regarding quantification were voiced and at the same time other commercially available NIRS systems were also under scrutiny[164 - 168], so the below experiment was conducted.

Method

NIR analysis during this experiment was carried out using a commercial spectroscope (Critikon 2020, Johnson and Johnson Medical) which has an emitter - detector separation distances of 13mm and 45mm. Data was continuously collected on laptop computer using Microsoft Terminal software.

Five adult male post mortem subjects (mean age 70.2 years) were studied. All measurements were conducted within five days of death. The cadavers were stored at $4^{\circ}C$ and the autopsy room is held at a constant temperature of $15^{\circ}C$.

A coronal skin incision at the vertix of the skull through all layers of the scalp was performed to facilitate sub - galeal dissection and peeling forward of the scalp to reveal the underlying skull. The bone was cut bilaterally with a plaster saw, the cut starting at the region of the pterion and passing posteriorly to the occipital protuberance. The anterior margin cut commenced at the region of the pterion and passed superiorly over the vertix of the skull to the opposite pterion. The bone was lifted off and any adherent meninges removed by sharp dissection (see fig. 6.1)

The brain was removed by sectioning the brainstem at the level of the foramen magnum, and was examined in the normal fashion by the pathologist.

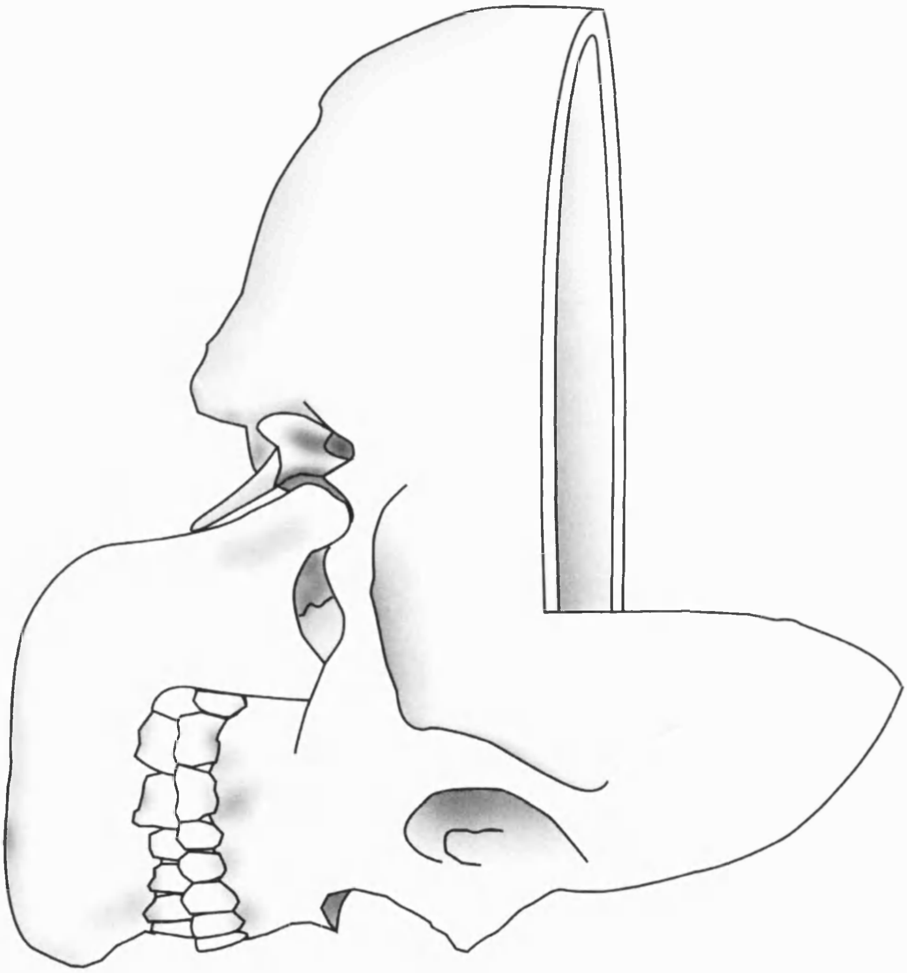
The cadaver was rolled through 180° to a prone position allowing the remaining skull to act as a bowl in which solutions of blood could be placed.

The NIRS sensors were securely placed as high as possible over the forehead avoiding the sphenoidal air sinuses. The forehead scalp remained fixed to the skull in the area where the sensors were located. The 2020 monitored was configured to measure 10 second samples and to output the ADC intensity levels for each wavelength and LED intensities at each detector to the computer.

Blood used in the experiments was "out of date" donated blood which has been screened for viral and bacterial contamination. The blood was fully oxygenated prior to use by bubbling air through it for 5 minutes.

All cadavers were studied using the same protocol. Baseline was achieved by assessing the skull cavity empty and then lined with black felt as a total absorber. The skull cavity was then lined with cling film as a substitute for a meningeal layer and filled with 250 ml of milk. Milk and intralipid have similar light scattering properties to brain tissue[89, 96]. NIRS measurements were recorded with the milk in the skull cavity then as the concentration of haemoglobin was increased in 1% steps from zero to 7% of the fluid volume by adding aliquots of oxygenated blood. Two recordings were made at each level of haemoglobin concentration. After the 7% measurements were completed the cling film and milk solutions were removed and replaced by a fresh layer of cling film and a further 250 ml of milk. The whole range of measurements was repeated again to give a total of three studies with cling film in situ. The process was then repeated except that no cling film was placed in the skull cavity. This gave a total of six recordings, three with and three without cling film.

Fig 6.1. Skull with bone removed



Data Analysis

Raw data was passed from the Critikon 2020 to laptops previously described. These files were then opened in Microsoft Excel 5.0 for analysis.

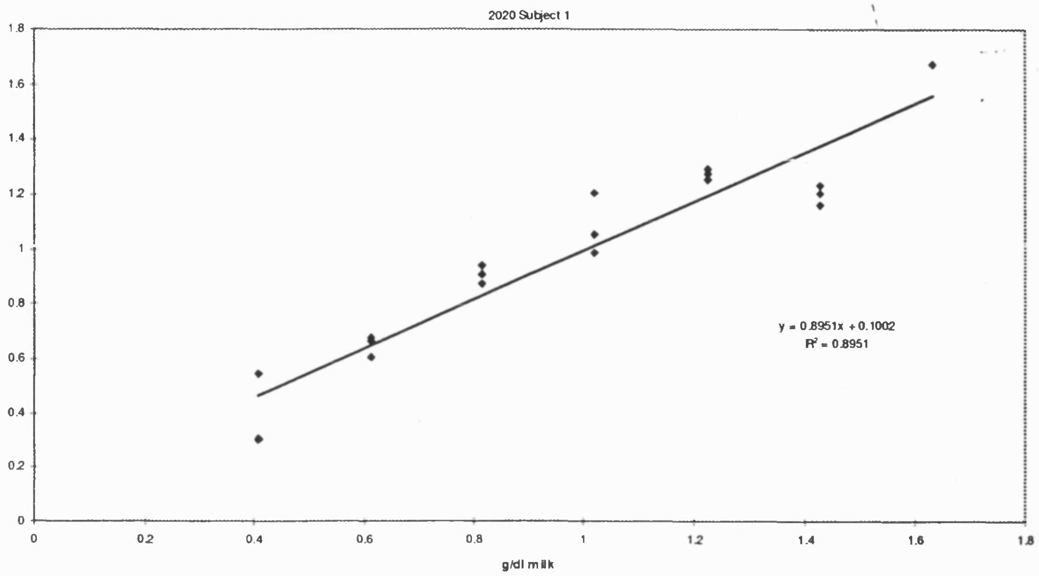
Initially the data were analysed using the existing 2020 algorithm based on the inverse matrix of the haemoglobin absorption coefficients. The data were then analysed using a least squares method available as a function in Excel (LINEST). This method calculates a straight line that best fits the data using a straight line equation $y = m_1x_1 + m_2x_2 + m_3x_3 + m_4x_4 + b$ where the x values are the negative LOG of the measured laser intensity ratios (channel 2/channel 1) for each wavelength and y is the known concentration of haemoglobin in the skull cavity.

The function provides a coefficient of determination, r^2 and a standard error in the measurement. The accuracy of the line calculated by LINEST depends on the degree of scatter in the data.

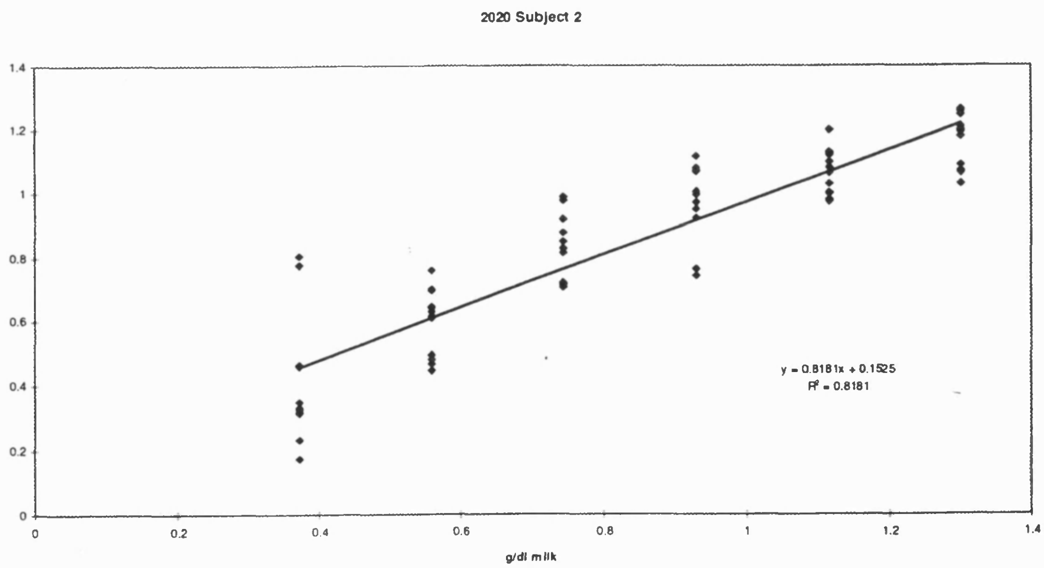
Results

Individual analysis of subjects by least squares analysis is demonstrated in graphs 6.1 – 6.5, with pooled data being shown in graph 6.6. Analysis by the standard Critikon 2020 algorithm (inverse matrix of haemoglobin absorption coefficients) is shown in graph 6.7. The correlation coefficient of individual subjects when analysed by least squares methodology varies from 0.903 to 0.969, but combination of all five subjects reduces this to 0.598. Analysis by the standard Critikon algorithm produced a pooled correlation of 0.239.

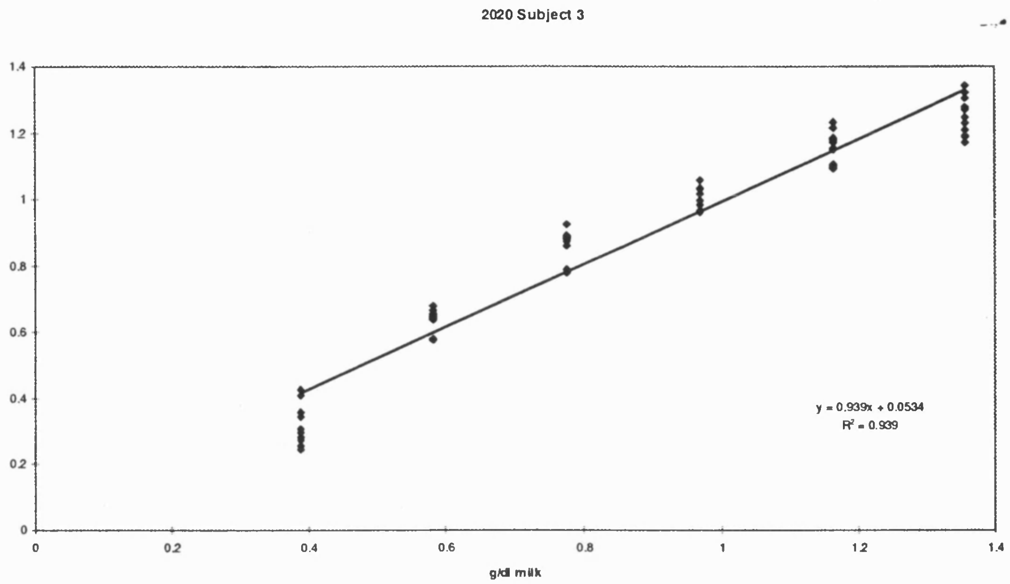
Graph 6.1. Subject 1, least squares correlation



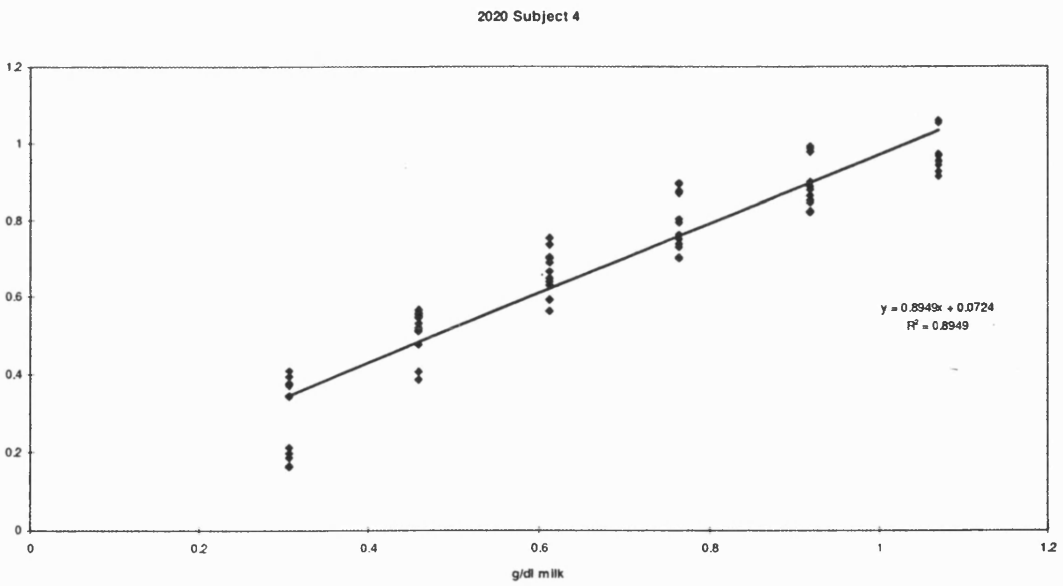
Graph 6.2. Subject 2, least squares correlation



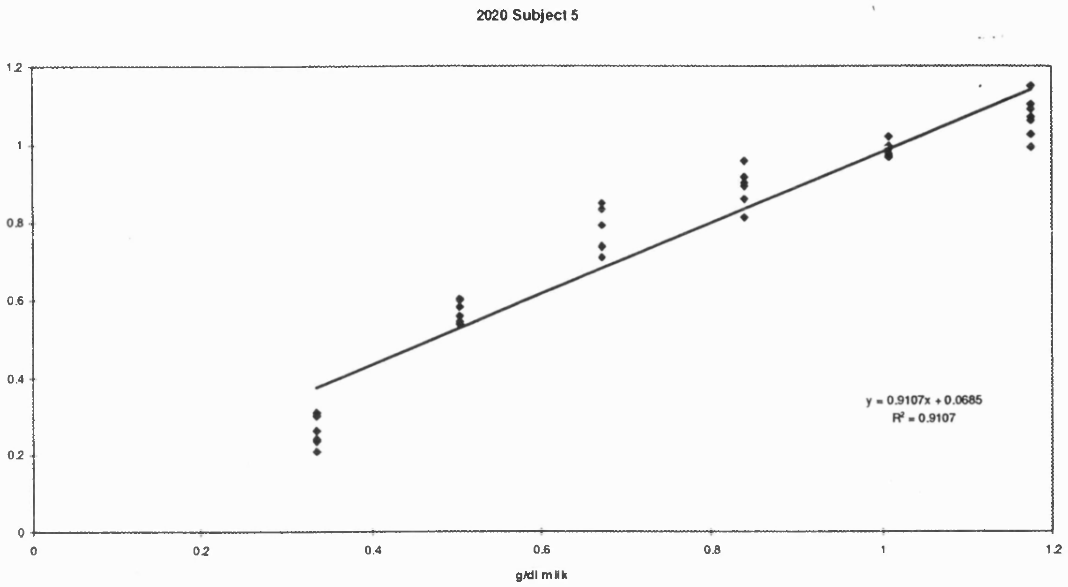
Graph 6.3. Subject 3, least squares correlation



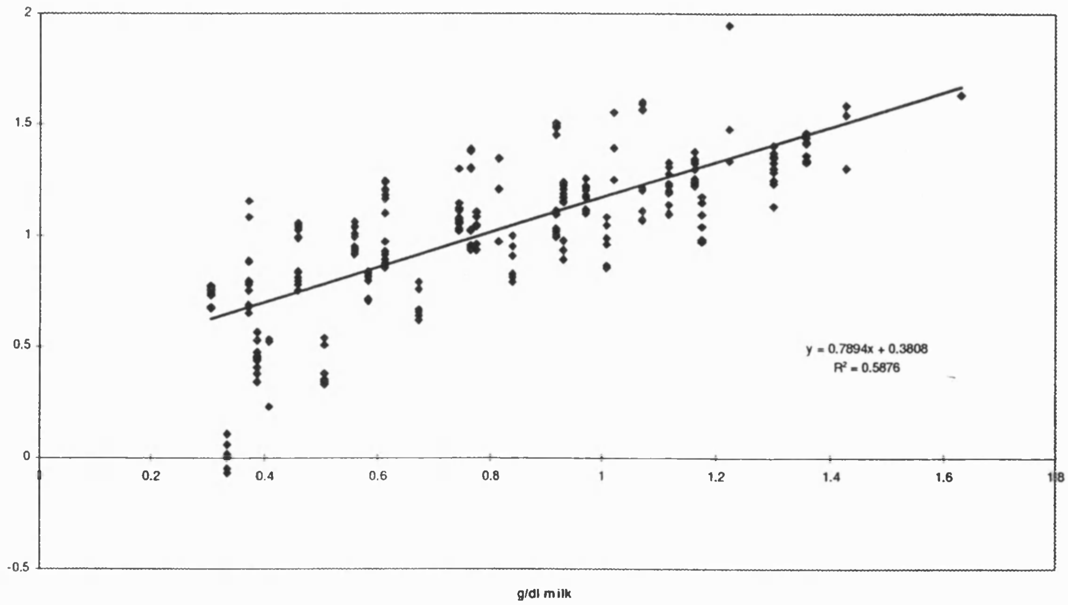
Graph 6.4. Subject 4, least squares correlation



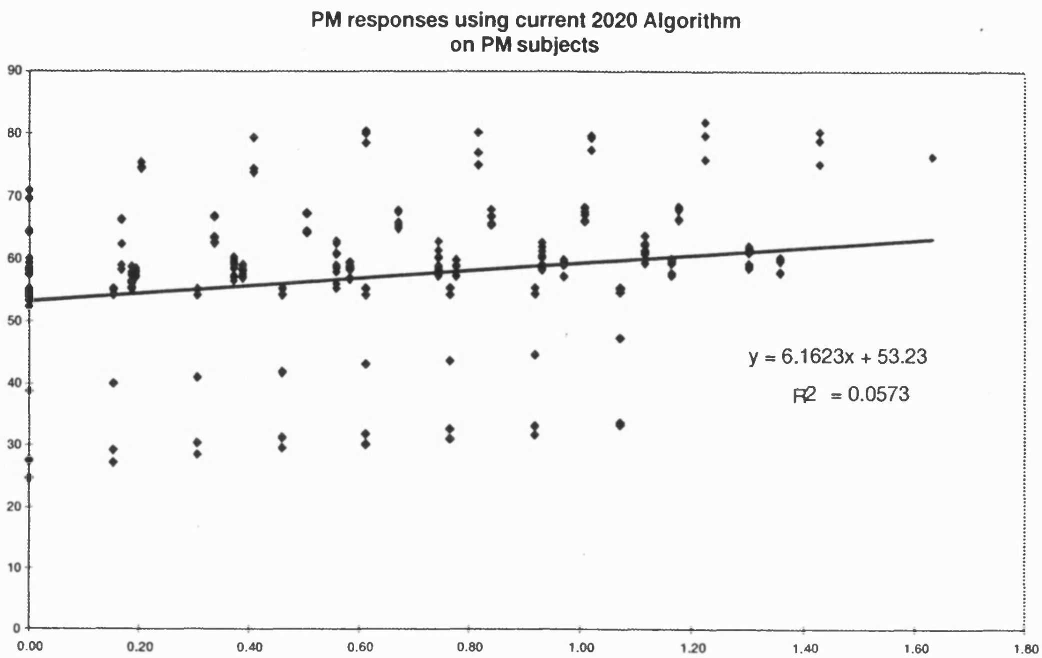
Graph 6.5. Subject 5, least squares correlation



Graph 6.6. Subjects 1 - 5, pooled data, least squares correlation



Graph 6.7. Subjects 1 - 5, pooled data, inverse matrix of haemoglobin coefficients



Discussion

The above experiment has several design faults which are "fixed"; firstly the temperature of the post mortem room was held at 15^{0}C, the cadavers and the fluids used was 4^{0} C. Obviously these temperatures are not compatible with life, however these temperatures are set to store the bodies without decomposition and cannot be altered.

The lower than normal temperature did not effect the electronic equipment, and since we were assessing haemoglobin concentration in milk and not its saturation, it will not change the results.

Secondly the anterior scalp left in situ was relatively bloodless due to dependency pooling over the occipital region. This is a natural physiological phenomena post mortem and cannot be avoided. For the purpose of this study having a bloodless scalp was an advantage and probably allowed us to obtain a "cleaner" signal with which to make a judgement regarding quantification. In a clinical setting the scalp blood flow would change with temperature and stress adding a further contamination to the cerebral signal[(165, 166)]. The subtraction of superficial from deep signal should go part way to reducing this, but there will be some effect. As well as the blood flow in the scalp there would be blood in the cranium which is not the case in this cadaveric model, although the subtraction system of the 2020 should again reduce the effect of this. These two factors mean that any data obtained from this experiment should be treated with some caution because it does not fully represent the situation that occurs in life where there is flow through both scalp and cranium.

Thirdly additional interfaces are created by small amounts of air being trapped between the scalp and skull, the cling film and dura. We have tried to keep these to a minimum by carefully excluding as much air as possible, but acknowledge that it must have some effect.

Lastly, the emulsion that the milk and blood form during this experiment has been assumed to be uniform, although the author accepts he did not test the mixture to ensure no clot formation or formation of protein complexes had taken place. Formation of clot or protein complexes would make each emulsion of unique composition and render comparisons between subjects invalid.

Despite this the model is as natural as can at present be created, and has the advantage of easy reproducibility in other centres for comparison of other types of NIR monitors, and to assess changes in either software or hardware design. One drawback to future cadaveric work is the change in cultural attitudes to post mortems in recent years. An alternative would be a large live simian model, where the scalp and cranium would have an ongoing blood flow and be more akin to the clinical setting, but this is unlikely to be ethically approved due to the suffering that would be caused by the destruction to the brain.

The good correlation between haemoglobin concentration and absorption in the same subject, which is replicable on repeated study, is encouraging and appears to prove that the 2020 system is capable of measuring changes in intra - cranial haemoglobin and consequently oxygenation. The stability of data recorded would seem to indicate that the pathlength of photons is constant once the probe is applied and secured in an individual and so should produce a meaningful representation of the change in cerebral oxygenation/haemoglobin with time.

The poor correlation across the group is disappointing and would indicate that quantification and creation of a normal range is at present beyond the system, even if the current inverse matrix algorithm were replaced by one using least squares. The reasons for inter - subject variation in clinical practice are multiple and are related to differences in the geometry of the patients' skull, variable thickness of the varying interfaces through which the NIR light must travel and effects of superficial tissues. This study has only been able to demonstrate the effect of skull geometry since the scalp was avascular and the interfaces common and uniform. Even so the single variable of skull geometry has had a profound effect with identical haemoglobin/milk mixtures producing markedly different absorption patterns, probably due to alterations in the path length of light through tissue, although as previously stated the emulsion may have separated and be non – uniform in composition. In clinical practice this variability will then be compounded by the additional effect of inter - patients differences in the interfaces occurring at scalp - skull, skull - meninges and the quantity of CSF around the brain, all of whom have the potential to cause scattering of light. Scalp and cranial blood flow is also different both across subjects and in the same subject in response to changes in temperature, stress and blood pressure; even with a subtraction system there will be photon absorption related to the superficial tissues that will make quantification even more difficult to achieve.

Achieving quantified measurements using the Critikon 2020 does not appear to be possible even with alterations in the algorithm. The system does have the ability to measure changes in haemoglobin concentration occurring with time and can produce a qualified (trend) trace. In the context of elective surgery where the patient is normal prior to induction of an anaesthetic or application of an arterial cross clamp then the system will be a valid monitor of changes in cerebral oxygenation with time. At the current moment identification of an "alarm limit" at which action must be taken to avoid neuronal damage is not possible, even with improvements in interpretative algorithm. This problem is not restricted to the Critikon machine[140, 141, 156, 157, 164 - 168, 170, 171] all research and clinical spectroscopes currently in use produce qualified data and much research is being conducted to try and overcome the large number of variables.

Conclusion

The model used in this study is as accurate a representation of the natural situation as can be currently achieved. The Critikon 2020 NIR system as it currently available does not have the capability of demonstrating quantified data and even with an algorithm change to least squares analysis this cannot be achieved.

However the system can demonstrate qualified change accurately and reproducibly with both the current algorithm, and even better with the use of least squares.

The Critikon 2020 NIR system therefore has the potential to be a useful clinical monitor in medicine in situations which are dynamic after a period to establish a normal baseline, but without quantification and "alarm limits" the application is limited and could not be recommended for transient monitoring of those whose cerebral oxygenation is of unknown status, such as in acute resuscitation.

Chapter 7 Frontal versus Temporal NIRS Monitoring

Introduction

Near infra-red spectroscopy has recently been introduced as a monitor of cerebral oxygenation in both the child by a transmission method and in the adult by the single or dual channel reflectance. In the neonates there is no controversy regarding probe position due to the transmission method of obtaining data, whilst in the adult being studied by reflectance the potential for probe position to effect results is unknown, although some authors have made recommendations based on the results they have achieved by comparison of NIRS with transcranial Doppler(172).
The advantages of the frontal position is its accessibility, patient acceptability, lack of interference with transcranial Doppler (if used) and ease of probe application and retention. The disadvantages that the underlying air sinuses potentially cause interference and add additional interfaces which can contaminate the signal by causing light scatter.
The advantage of the temporal position is that it theoretically yields information from the temperoparietal region which is supplied by the middle cerebral artery, which is both the direct end artery of the internal carotid and the vessel that is commonly studied by transcranial Doppler. The bone here is the thinnest of any part of the skull and does not contain any air sinuses. The main disadvantages are the requirement for the patients to have a limited head shave, the difficulty in securing the NIRS probe for the duration of the investigation and the competition for access with a TCD probe.

Despite the above mentioned advantages and disadvantages the most important factor with probe position is the quality, reliability and usefulness of data obtained so that the operating surgeon can make valid judgement on condition of the cerebral circulation. To date no - one has successfully measured traces from both sites simultaneously during carotid surgery although McCollum(172) tried and failed due to interference between Invos 3100 probes and so no data is available on which site should be recommended.
This study was conducted to assess which site was easiest to use, easiest to maintain throughout the procedure and, most importantly, gave reliable data recordings which were accurate.

Method

Ethical approval was sought and obtained from the local ethical committee. All patients gave written informed consent prior to the operation and application of probes.

Critikon 2020 near infra-red spectroscopes (Johnson and Johnson Medical) connected to laptop computer via an RS232 port were used, the probes being placed at both the frontal and temporal positions of the cerebral hemisphere being supplied by the carotid artery undergoing surgery. A limited head shave was required to apply temporal probe. Both probes were then held securely in place by the use of a headband, initially one supplied by the manufacturer and then using elastoplast. Data was stored and interpreted using software supplied by the manufacturer (Datalogger, Johnson and Johnson Medical). The Datalogger recorded information on changes in oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb) and cytochrome aa_3. From this the level of total haemoglobin (tHB) and regional saturation (rSO_2) were displayed. The regional saturation has been used for comparison of frontal and temporal probes.

A 2MHz transcranial Doppler probe (Scimed) with specialised head band was applied to all patients who were found to have a temporal window in pre - operative assessment.

A precalibrated jugular venous saturation catheter (Abbott Laboratories) was inserted in the ipsilateral internal jugular vein by open technique during surgery in forty patients.

All patients had invasive blood pressure monitoring by arterial line, non invasive blood pressure monitoring by automated sphygnomanometer, pulse oximetry and ECG monitoring whether they were under a general or locoregional anaesthetic. Therapeutic manoeuvres to maintain blood pressure were undertaken as appropriate by the anaesthetist using a variety of pharmacological agents best suited to the cardiorespiratory status of the individual patients.

Results

Fifty three patients were recruited between 1996 and 1997 in Bath, fifty two endarterectomies and one aneurysm. Thirty two of the endarterectomies were performed under local anaesthesia and twenty under general anaesthesia. The single carotid aneurysm received their operation under a general anaesthetic.

Application of both frontal and temporal NIRS monitoring was attempted in all patients as was the application of a TCD probe in those found to have a window pre - operatively. The manufacturers headband provided for the NIR spectroscopes was found to be inadequate and caused difficulty with application of the TCD headband and so was abandoned very early on in the study and was replaced by the use of elastoplast. This held the probes firmly in place but did cause problems with perspiration and was difficult to remove at the end of the procedure without causing pain.

Jugular venous bulb monitoring was used in the first forty patients but then discontinued since it did not add any additional information and was found to be a poor dynamic measure of cerebral oxygenation.

Data acquisition occurred as follows (see table 7.1); adequate near infra-red signal was obtained in 45 (87%) patients at the frontal sides and 38 (72%) at the temporal. Trans - cranial Doppler signal was obtained in 42 (80%) patients. NIRS probe failure was more common in females than males for both frontal and temporal sites (frontal, 4/13 versus 3/40; temporal, 5/13 versus 9/40)

Lack of a TCD window occurred in 11/53(20%), again more commonly in females than males (8/13 versus 3/40).

NIRS probe failure rates were similar regardless of the presence or absence of a TCD window (frontal, 5/42 versus 2/11; temporal 10/42 versus 4/11).

Application and removal of clamps to the common, internal and external carotid resulted in changes in the NIRS trace at both the frontal and temporal sites, with the changes in NIRS trace being time related to the clamping maneovure, indicating that it was a real phenomena rather than artifact. Clamp application to the external carotid artery caused similar decreases in cerebral saturation at both probe sites (frontal range 0 – 3.5%, mean 1.7%;

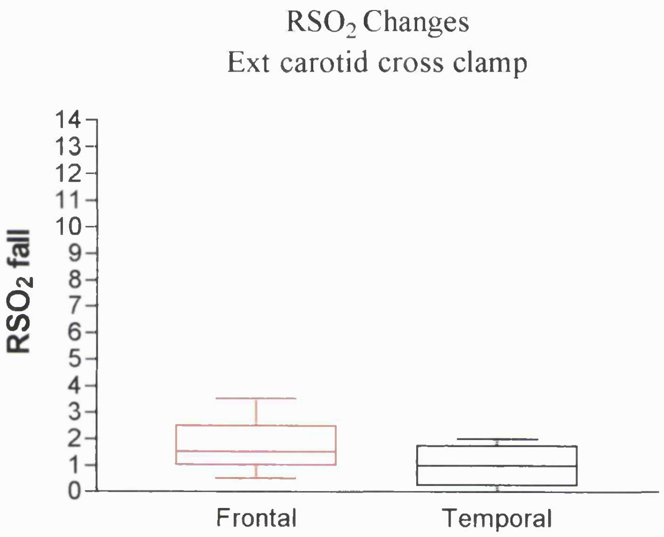
temporal 0 - 2%, mean 1.25%), see graph 7.1. Surprisingly these changes were significant when analysed by a two tailed unpaired t – test, p = 0.039.
Clamp application to the internal carotid caused markedly different responses (frontal 0 - 7.5%, mean 3%; temporal 0 - 2%, mean 1%), see graph 7.2, but without stastically significant difference, p = 0.06. Larger changes were seen with clamp application to the common carotid (frontal range 0 - 14%, mean 3.5.%; temporal 0 - 8%, mean 2%), see graph 7.3, once again these changes did not reach significance, p = 0.23.
Shunt insertion caused a rise in regional saturation at both sites (frontal range 0 - 6%, mean 3.3%; temporal 0 - 3%, mean 1.3%), see graph 7.4, but here there was a significant difference between the two sites, p = 0.036.

Similar changes occurred at the end of the procedure. Shunt removal caused regional saturation to fall (frontal range 0 - 6%, mean 4.8%; temporal 0 - 2.5%, mean 1.2%), see graph 7.5, but the number of recordings is too small to make a valued judgement. Clamp removal caused regional saturation to rise, the external carotid changes again being similar at both probe sites (frontal 0 - 4%, mean 1.75%; temporal 0 - 4.5%, mean 1.5%), see graph 7.6, p = 0.54. The internal (frontal 0 - 13%, mean 3%; temporal 0 - 2.5%, mean 1%), see graph 7.7, again did not reach significance, p = 0.09.

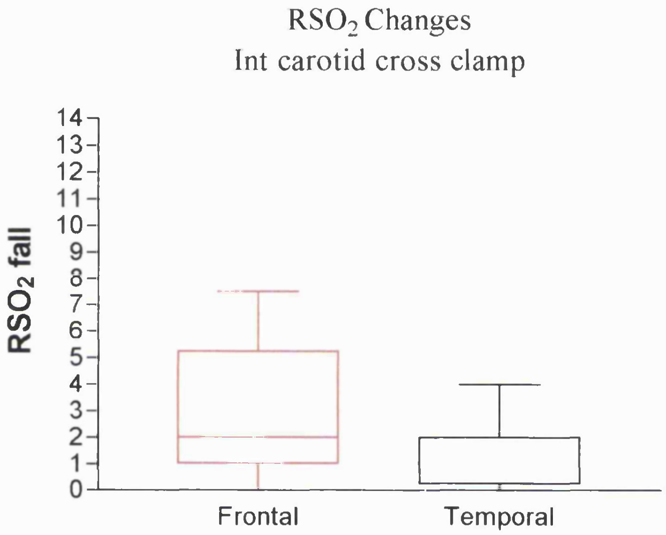
Table 7.1. Rates of successful recording by site, type and gender

Monitor	**Male**		**Female**	
	Success	Failure	Success	Failure
TCD	37	3	5	8
NIR (frontal)	37	3	9	4
NIR (temporal)	31	9	8	5

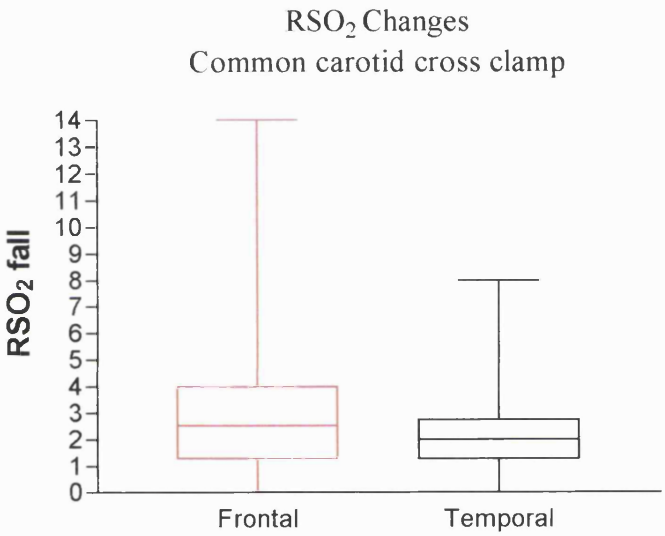
Graph 7.1. Changes with external carotid cross clamp, temporal vs frontal



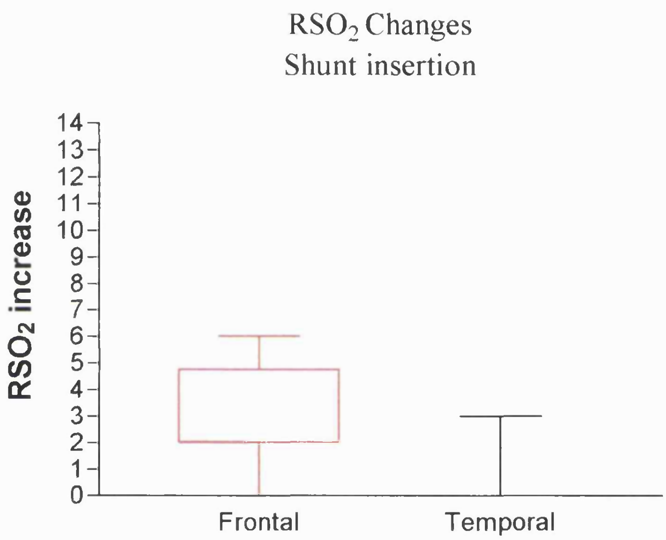
Graph 7.2. Changes with internal carotid cross clamp, temporal versus frontal



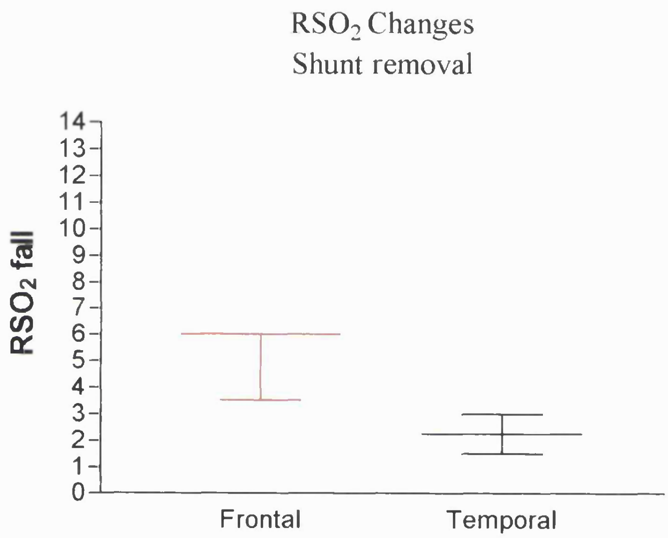
Graph 7.3. Changes with common carotid cross clamp, temporal versus frontal



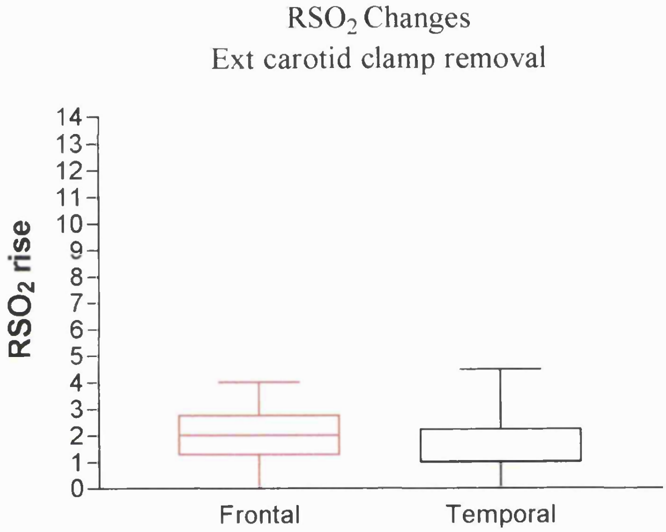
Graph 7.4. Changes with shunt insertion, temporal versus frontal



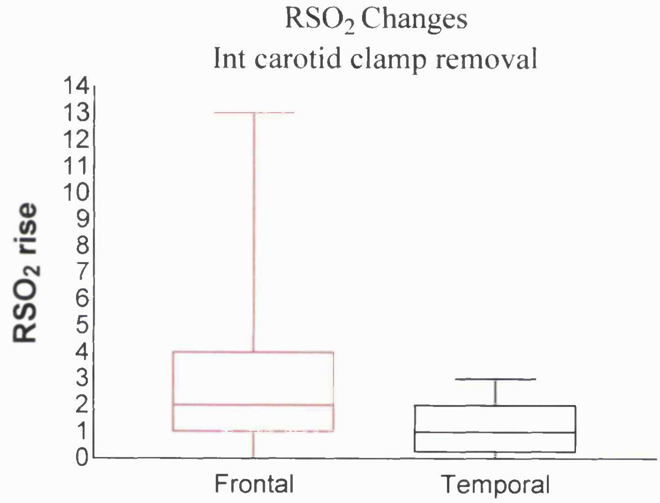
Graph 7.5. Changes with shunt removal, frontal versus temporal



Graph 7.6. Changes with external clamp removal, frontal versus temporal



Graph 7.7. Changes with internal clamp removal, frontal versus temporal



Discussion

The purpose of this study was to assess whether it was possible to successfully monitor changes in cerebral saturation at two different probe sites and obtain clinically useful information. This has been achieved at both probe positions and in the presence of another monitor (TCD) which was competing for space. The equipment was easy to use and did not fail due to electrical or mechanical breakdown and patients under locoregional anaesthesia did not complain about application of the system. The data recorded was stable in the majority of cases and seemed reliable. Different changes in cerebral oxygenation were seen in the frontal compared with temporal probes, although not always of statistical significance, which gives credence to the theory that there are regional differences in cerebral blood flow. The regional differences in change with external carotid clamping was more surprising but could be explained by either varying scalp or cerebral collateral supply from the external carotid.

The overall design of the study suffers from a lack of a power calculation prior to commencement, which means that despite the achievement of statistical significance the conclusions must be treated with caution since the number of subjects involved is small. The failure of the temporal probe to record in over one quarter of patients despite a head shave and the use of an adhesive head bandage was disappointing and did not appear to be related to a "learning curve" since latter cases suffered from the same problem. Grease present on the scalp was thought to be in part responsible but even after rigorous cleaning with alcohol solutions to dry the area the surface contact was at best variable. Potentially recording could be improved by a more radical removal of hair and a pre operative hair wash with blow drying to remove grease and moisture, but this is unlikely to be acceptable to patients, especially ladies. We found that patients in the pre – operative phase were more concerned about the potential for stroke than any concerns over their hair and were happy to have additional monitoring which could be of benefit. Once the surgery was over and successful they were quite distressed about their appearance and so a more radical shave is not to be recommended.

The 13% failure rate of the frontal probe is far better than both the temporal NIRS and the TCD and in future clinical practice should be even better since in two (4%) cases the inability to record was related to software problems rather than any problem with the NIRS system. Also abandoning the inadequate headband supplied with the systems and replacing it with elastoplast will avoid slippage of the probe and so should reduce failure further. The lower failure rate is likely to be related to the absence of hair over the frontal region and it is likely that with increased experience successful monitoring will approach 100%.

Changes with clamping of the external carotid have confirmed that despite the two channel subtraction method used by the Critikon 2020 there is still an element of interference caused by the scalp blood supply. The magnitude of this interference is non significant in the majority of cases, but in 9 (18%) cases it accounted for a change in RSO_2 greater than 2%. One patient in this study who underwent surgery by local anaesthesia had shunt reversible neurological dysfunction after a 2% change in RSO_2 and so this should be considered to be a significant degree of interference.
Of course, the changes may be due to the collateral supply that the external carotid is known to give to the brain and so it is possible that this is a rise in cerebral oxygenation rather than signal contamination. Scalp blood supply can be totally excluded by the use of a scalp tourniquet which would allow collateral versus contamination argument to be settled. The main drawback of a tourniquet is the competition for position with the TCD. Alternatively the operating surgeon can apply the external and internal clamps separately with time allowed for the monitor to return to a new baseline from which to make a judgement regarding the change in cerebral oxygenation.

The changes seen at application of the internal carotid clamp can be considered to be a purely cerebral signal since time was given to allow the trace to stabilise after application of the external clamp and so the cutaneous supply should be constant and any collaterals eliminated. The time relationship between clamp application and change in RSO_2 was concurrent and seen simultaneously at both frontal and temporal probes. When NIRS and TCD were recorded simultaneously, the changes in RSO_2 were mirrored with changes in cerebral blood flow, although these do not correlate since the systems are measuring entirely different aspects of cerebral perfusion.
The magnitude of change was greater at the frontal probe in addition to being more

frequently obtainable. Similar changes were seen where the common carotid clamp was applied as the first maneovure, but it must be remembered that in this situation there is bound to be an element of external carotid contamination and so the magnitude of change should be treated with some caution. Shunt insertion and removal, obviously a purely cerebral phenomena, also mirrored these changes. In view of the time relationship with TCD it would appear that the NIR systems are measuring a true change in cerebral oxygenation. The larger magnitude in change seen at the frontal site are probably related to that site being a superior monitoring position, but may be related to regional changes in cerebral oxygenation or to the air sinuses causing signal scatter or tracking of photons along the bone interfaces.

Blood pressure was measured both invasively and non – invasively by the anaesthetist during the course of the surgery, with pharmacological interventions undertaken to maintain systolic pressure within limits agreed for the individual patients between the operating team. This data has not been included in this thesis, nor has it been analysed to assess whether the changes seen in TCD, NIRS or JVS can be related to alteration in blood pressure alone. The author accepts that this is a serious oversight since cerebral perfusion is directly related to mean arterial pressure in the presence of stable intra – cranial pressure.

Comparison of frontal and temporal sites has shown that successful monitoring occurs more frequently at the frontal site but that there is little difference in the changes in RSO_2 measured at the two sites other than in the small number of cases where a shunt is used, where shunt insertion and removal have significantly larger degrees of change seen at the frontal site. Overall it would seem sensible to recommend monitoring with a solo frontal probe since it is easier to apply, easier to maintain and measures RSO_2 at least as well if not better than the temporal probe.

The failure of the jugular venous saturation probe to give reliable recordings was a disappointment, we believe the problem with JVS was that the probe would lie adjacent to the vessel wall and so not give an accurate measure of the venous saturation. This was overcome by intermittent manipulation, but this required cessation of surgery which rather defeated the object of having a monitoring system. Once again this was not restricted to the early cases and so appears to be an inherent fault with the system rather than one which is operator dependant.

The main drawback with both probe positions used in this study and all NIR literature to date is that no investigator has monitored the occipital region. This area is not supplied directly by the internal carotid, but some supply will reach this area via the Circle of Willis. Some feel it is a reduced supply to the hindbrain which causes the immediate and profound deterioration in neurological function on carotid cross clamping under locoregional anaesthesia which is reversible by the insertion of a shunt. This deterioration is related to hypoxia rather than embolisation and so should be measurable by NIRS. To fully investigate this one would need to monitor at frontal, temporal and occipital areas. The thickness of the bony skull at this point may be too great for the NIR signal to obtain a successful and accurate recording, plus the area interrogated may not necessarily be representative of changes in the occipital region as a whole. Even if it were technically possible it would require an extensive head shave and the purchase of three spectroscopes and computers, with cost implications for the surgeon and cosmetic issues for the patient.

Conclusion

Near infrared spectroscopy is capable of recording changes in regional saturation in underlying tissues. Despite the dual channel system employed by the Critikon 2020 there is an element of contamination by the scalp, but this can be minimised by staged clamping of external then internal arteries. If staged clamping is not used the degree of scalp interference could lead to the unnecessary insertion of a shunt. The frontal probe position is superior to the temporal since it does not require a head shave, appears to give a better signal and has a lower failure to record rate. Overall the frontal probe performed better than either TCD or a temporal NIR probe in this study with a superior recording rate. If NIR is to be used as a monitor during carotid surgery we would recommend it is used at the frontal position.

Chapter 8 Changes in cerebral oxygenation in response to intra - operative emboli during carotid endarterectomy

Introduction

An embolus is defined in Dorland's Medical Dictionary as a mass of clotted blood or other formed elements (air bubbles, calcium fragments etc) brought by the blood from one vessel and forced into a smaller one, thus obstructing the circulation. Depending on the site of the obstruction the patient may or may not have any symptoms.

Peri - operative cerebral complications are known to occur during carotid endarterectomy which may be caused by either hypoperfusion and hypoxia or by embolisation. The former can be avoided by the maintenance of blood pressure during the procedure and the use of a carotid shunt, whilst the latter may occur even in the most careful performance of surgery. In an effort to reduce the risk of embolisation most surgeons continue the patients on anti – platelet therapy and give a bolus of intravenous heparin prior to clamp application. Experimental work using artificially produced air bubbles of known size has shown that doppler is capable of detecting air particles as small as 50μm when moving in a blood substitute media[(175)]. Studies of those with an embolic focus (carotid plaque, cardiac arrhythmia, valvular disease etc) has shown a large number of ipsilateral and contralateral embolic events, which are absent in healthy controls [(106, 176)], indicating that they are a real phenomena rather than artifactual. Use of intra - operative transcranial Doppler during carotid endarterectomy has allowed operating surgeons to continually assess the flow of blood through the middle cerebral artery, assess the effect of carotid cross clamping, monitor shunt patency and to note if embolisation has occurred[(99 - 108)]. Transcranial doppler detects both particulate and gaseous emboli, but it is the former that are associated with cerebral events[(58-60d)]. Outcome is not solely related to the presence of emboli but also the number and duration since a large intra - operative embolic load is known to be associated with a poor outcome, whilst continued post operative embolisation is an indication for anticoagulation or return to operating theatre[(99, 108)] for exploration of the operative site for the presumed clot at the site of surgery. Discriminating between particulate and gaseous emboli is not possible by listening to the audio signal of the TCD, but can be achieved by analysis of the spectral pattern[103]. Gaseous emboli cause high peaks on the TCD trace whilst particulate emboli cause drops in the signal. Unfortunately this is a retrospective process that does not assist during the performance of surgery and is still a research tool limited to a small number of centres.

From this it can be seen that although TCD can detect emboli on its own it does not have the ability to differentiate gaseous from particulate matter during an operation and so adjust surgical technique or anticoagulated the patients. If one were to combine another cerebral monitoring system with TCD then one could potentially detect emboli in real time. Significant embolic insult resulting in a neurological deficit should render an area of cerebral tissue hypoxic or ischaemic. One can detect this change in cerebral oxygenation either regionally or globally. Global assessment can be achieved by the use of a jugular venous saturation probe whilst regional saturation can be assessed by the use of near - infrared spectroscopy.

Previous work[176] involved the use of a different NIR system (Invos) in a small number of patients undergoing carotid angiography. This procedure is associated with embolisation measurable by TCD[177], but with a much lower incidence of neurological injury (<1% versus 3% in carotid endarterectomy) and not surprisingly no alteration in cerebral oxygenation or neurological deficits occurred in the study.
One therefore did not feel this negative research precluded performance of the following study which was designed to assess whether combining an emboli detection system (TCD) with assessment of regional and global cerebral oxygenation (NIRS and JVS) would allow identification of significant embolic load in real time rather than retrospectively.

Method and Materials

Ethical committee approval was sought and obtained, all patients gave informed written consent prior to surgery.

Patients undergoing a local anaesthetic received oral premedication on the ward one hour prior to surgery with 30mg Temazepam and 25mg Phenergan. Patients undergoing a general anaesthetic received premedication appropriate to their co - existent medical problems on the day of surgery.

All patients had intravenous access established and invasive blood pressure monitoring with an arterial line regardless of the anaesthetic employed. All patients have skin infiltration from the Tragus of the ear along the anterior border of sternocleidomastoid to the Sternal notch with 0.5% bupivicaine plus adrenaline. Patients receiving local anaesthetic have an additional cervical block placed from C2 to C5, again with 0.5% bupivicaine plus adrenaline.

A limited head shave of the ipsilateral Tempero - Parietal area above and behind the ear was made, and one NIRS probe placed here and one just inferomedially to the hair line of the ipsilateral Frontal area. The probes were then attached to their respective monitors (Critikon 2020, Johnson and Johnson) and signal adequacy assessed. Recordings were transferred to 486 laptops preloaded with specialized software (Datalogger, Johnson and Johnson) throughout the procedure.

An ipsilateral transcranial Doppler probe (PC - Dop, Scimed) was placed over the Temporal window in the normal fashion, with audio signal recording taking place throughout the procedure. A head box was employed to protect the probe in anaesthetised patients and a specialised drape arrangement in those under locoregional blockade.

The patient was placed on the operating table and general anaesthesia (if used) induced. The patient was positioned with a sandbag under the shoulder and a headring to gently extend the neck.

After dissection of the Carotid sheath a precalibrated JVS catheter (Opticath, Abbott Laboratories) was inserted and passed cephaled to the Jugular bulb.

Recordings from all three monitoring systems were made for the duration of the operation, and events such as clamping and shunting marked on the Datalogger software. Single embolic "blips" on the trace were not assessed, nor was the total number of events per

procedure counted, rather runs of emboli were noted and recorded to assess if there was a temporal association between emboli and a change in regional or global oxygenation.
Post closure of the endarterectomy a Duplex scan of the operative site was performed to exclude technical inadequacies.
At the end of the procedure all data was transferred to a computer spreadsheet (Microsoft Works) for graph production and analysis.

Results

53 carotid procedures were performed in the study period 1996 – 1997 at The Royal United Hospital in Bath, 52 endarterectomies and 1 aneurysm on 41 male and 12 female patients of mean age 66.5 years (45 - 84). 32 endarterectomies were performed under a local anaesthetic and 20 under a general, the aneurysm received a general anaesthetic.

Recordings were complete from the frontal NIRS probe in 46 cases, and from the temporal in 39. No transcranial window was available in 11 patients, with no additional irretrievable signal loss due to technical problems. JVS recordings were unreliable in 6 cases.

Nine episodes of emboli occurred; eight at clamp release post endarterectomy and one due to an abnormally functioning shunt which was subsequently changed. In five of the cases the emboli were of duration <1 second, with < 3 embolic events detected. In the remaining three cases the duration of emboli was 5 seconds, 50 seconds and 80 seconds and the number of embolic signals recorded 8, 60, and 76 respectively. No changes in either NIRS probe or JVS saturation occurred during this time, indicating that cerebral oxygenation, both regionally and globally, was unaffected.

Discussion

Carotid endarterectomy is now a firmly established procedure in surgery, which may become more frequently performed if the current indications are expanded to include the asymptomatic patients. For benefit to be achieved the complication rate of surgery must be minimal and hypoxic insult by either hypoperfusion or embolisation avoided. This can be achieved by meticulous surgical technique, per - operative anticoagulation, use of shunts, end of procedure quality control and intra - operative monitoring. Despite use of all the above the incidence of embolisation was one in six in our study, possibly explaining why a neurological complication rate of approximately 3% is still present at the best centres.

Fortunately none of the patients had a clinically detectable deficit, explainable in several ways; firstly that the emboli detected to date are insignificant and did not cause any ischaemia or neurological damage, so both regional and global oxygenation remained unchanged. To assess this[31] would have required us to perform MRI scans pre and post – operatively and note any areas of infarction related to emboli, which would have been ideal but was not possible due to constraints of both finance and logistics.

Secondly that the emboli were gaseous and not particulate and so less likely to have an effect. To assess that would require the previously mentioned spectral analysis system, which is not at present available to us, however gaseous emboli should not occur during times of dissection or after clamps have been applied due to the system being closed. One presumes that the emboli heard at these times were probably particulate, but accept that those associated with a malfunctioning shunt may well have been gaseous.

Thirdly that they did cause subclinical ischaemic damage at a site in the brain which our monitoring systems did not detect; as was mentioned in the previous chapter we were only monitoring at two sites and so could be missing ischaemia at other sites. Additionally we did not enlist a neurologist in examining the patients and so very subtle signs of damage may have been missed.

Fourthly, the rate of embolisation we encountered was low, possibly as a result of good surgical technique, or more likely due to the small numbers of patients enrolled. Once again a power calculation had not been performed prior to commencement of data collection, if it had it would have shown several hundred patients needed to be recruited;

this is because the anticipated stroke rate is only 3 – 5%, but not all these injuries are due to emboli. Additionally 15% do not have a window for transcranial Doppler.

Lastly the limit of tissue interrogation by NIRS is the first few millimetres of the grey matter in the region below the scalp on which it is positioned. In situations such as cross clamping where the blood supply falls dramatically one anticipates that NIRS will change since the RSO_2 will alter over a relatively large region of the brain supplied by the middle cerebral artery; with embolisation the change will be specific to a smaller area and so is most likely to be outside of the zone of interrogation of the spectroscope. In view of this it probable that NIRS will only change if there is a massive and catastrophic embolic event.

Taking the methodological inadequacies and the limit of the technology applied, the author accepts that this experiment is at best a small pilot study that has demonstrated no clear results. The likelihood of NIRS changing with emboli is small and the use of the system for the purpose of emboli detection does not appear valid, confirming the previous finding in carotid angiography[(176)]. In view of this, future studies of the effect of emboli in carotid surgery would best be conducted in multiple centers so that adequate recruitment can be achieved within a realistic time – frame, with involvement of neurologists so that minor degrees of neurological dysfunction can be recorded.

Conclusion

Emboli during carotid surgery are frequently encountered, however in the absence of a real time method of assessing the significant from insignificant signals there is little the operating surgeon can do except perform surgery by meticulous technique. The addition of regional and global oxygenation measurement has not revealed any evidence of significant ischaemia to date.

Chapter 9 Near - infrared spectroscopic changes in carotid surgery under locoregional anaesthesia

Introduction

Ramsay Hunt noted the relationship between extra cranial carotid disease and cerebral infarction nearly one hundred years ago but it was not until the 1950's that the first successful surgical procedures for stroke prevention took place[3, 8, 9]. Of the techniques pioneered only endarterectomy has been proven in randomised prospective trials to be of benefit and is now established in vascular practice[19, 20, 23, 25].

The efficacy of the technique is dependent on the peri - operative complication rate being lower than the natural course of the disease on maximal medical therapy. Emboli and hypoxia are two of the common processes which may cause neurological damage. Application of the carotid cross clamp may lead to cerebral hypoperfusion and hypoxia, which if left unreversed for a prolonged period may lead to an iatrogenic stroke. In - dwelling shunts are available to restore blood flow, but their insertion can be difficult and may cause damage to the vessel wall[80]. Three approaches are thus available to the operating surgeon: to never use shunt, to always use a shunt, or to selectively shunt[12, 72, 76, 80]. Those who selectively shunt usually do so on the basis of a change in clinical condition in local anaesthetic procedures or a change in an intra - operative monitor which can measure cerebral blood flow, electrical activity or cerebral tissue oxygenation (see table 9.1). Selective shunting would appear the most attractive since only approximately 15% of patients require shunt insertion[71], but it depends the availability of a reliable, reproducible and accurate monitor of cerebral function with established criteria at which to intervene. As yet no system has all these features.

Near - infrared spectroscopy (NIRS) is the latest monitoring system used during carotid surgery and does not have an established threshold for intervention.

Clinically NIRS has been used to variable success by several authors in patients undergoing Carotid surgery and neurosurgery[148, 151, 154, 155, 157, 160, 161]. No major study has yet been performed looking at the level of desaturation that the brain can withstand prior to the onset of symptoms in those with diffuse atherosclerosis, but by comparing it with other more established monitors, primarily transcranial doppler, a desaturation of 10% has been proposed as significant (Prof McCollum, Aspects of Cerebral Perfusion, 1996). The following study was designed to try and identify the magnitude of desaturation at carotid cross clamping which is associated with neurological deterioration in patients undergoing carotid endarterectomy using locoregional anaesthesia.

Material and methods

The study was completed over two years in two centres, Bath and Coventry.
Fifty three cases performed under locoregional anaesthesia are included in this paper.
Patients were premedicated on the day of surgery with 20mg Temazepam.
On arrival in the anaesthetic room an ECG and a pulse oximeter were applied. IV access with a 14 gauge cannula was obtained. An arterial line was placed in the ipsilateral upper limb to the side of surgery.
A superficial cervical block along the anterior border of sternocleidomastoid with 15 - 20mls of 0.5% Bupivicaine plus 1:200 000 adrenaline was inserted, followed by a deep cervical block with 3 - 5mls of the same local anaesthetic at each of the levels C2 - C5.
NIRS monitoring was performed using the Critikon 2020 system (Johnson and Johnson Medical UK Ltd) which was placed in 53 over the ipsilateral forehead, with a second sensor being placed over the contralateral forehead in 11 cases and the ipsilateral temporal region after a limited head shave in a further 33 cases. The sensors were held in place using surgical adhesive tape wrapped round the head to create a headband or using Tubifast elastic bandage.
The patient was transferred to an operating table and positioned with the neck extended and a head ring in place. After draping a linear incision to facilitate dissection was employed with 1% Prilocaine used for additional local anaesthesia. In 20 cases a precalibrated jugular venous saturation (JVS) probe was placed in the ipsilateral jugular vein and connected to a continuous digital monitor (Opticath, Abbott Laboratories).
2500 - 5000 units of intravenous Heparin was given 2 minutes prior to cross clamping.
Carotid clamps were applied in the following sequence: external, internal and common, with time being allowed between external and internal application to allow the effect of scalp changes to be observed. All events were marked using Critikon Datalogger software (Johnson and Johnson Medical UK Ltd). A shunt was inserted only if neurologically indicated and this was also marked on the trace, as were periods of shunt clamping.
Standard endarterectomy with selective Dacron patching was performed. After completion of the anastomosis, backbleeding and washout with heparinised saline was performed.
Cross clamps were removed in the order external, common and, after a short period, internal carotid.

Data recorded during the operation was exported to spreadsheet for review and graph production with statistical analysis being performed using GraphPad Instat and GraphPad Prism.

Results

Successful monitoring was achieved in 45/53 (87%) at the ipsilateral frontal, 19/33 (58%) at the ipsilateral temporal and 11/11 (100%) at the contralateral frontal. Failure of monitoring was due to the probe falling off, usually due to excess sweating by the patient causing the adhesive tape to lift away. Shunting was required in 8/53 (15%) of cases because of deterioration in level of consciousness with shunt insertion being associated with improvement in clinical condition. Desaturation in the internal carotid traces are shown in table 9.2 and displayed graphically in figure 9.1 for the temporal probe and figure 9.2 for the frontal probe.

The mean desaturation in the ipsilateral temporal probe of those with neurological compromise and the need for a shunt was 3.5% (range 2 - 8%, standard deviation 2.14%) and in those with no neurological deficit 2.07% (range 0 - 8%, SD 1.86%), which is not statistically significant (two tailed unpaired t – test, $p = 0.2105$).

The mean desaturation in the ipsilateral frontal probe of those with neurological compromise and the need for a shunt was 6.44% (range 2.5 - 14%, SD 3.57%) and in those with no neurological deficit 2.34% (range 0 - 7%, SD 1.56%), which is statistically significant ($p<0.0001$, two tailed unpaired t - test).

Jugular venous saturation monitoring was achieved in 20 subjects, 2 of whom required a shunt. The patients who were shunted had a decrease in venous saturation of 10 - 15% (mean 12.5%, SD 2.5%) whilst those not requiring a shunt had a decrease of 0 - 12% (mean 2.4%, SD 4.18%), again being statistically significant ($p<0.05$, Mann Whitney U test), see table 9.2 and figure 9.3.

Graphical illustration of bifrontal traces had shown three types of desaturation (figure 9.4); type 1, no change in either trace (seen in 2/11 patients); type 2, desaturation in the ipsilateral hemisphere only (seen in 7/11 patients); type 3, desaturation in both hemispheres (seen in 2/11 patients). Shunts have been required in neither of the patients with type 1 desaturation, 1 of 7 patients with type 2 desaturation and 1 of 2 patients with type 3 desaturation.

Table 9.1. Commonly used intra – operative monitors of cerebral function

MONITOR	**ADVANTAGES**	**DISADVANTAGES**
STUMP PRESSURE	CHEAP	ACCURACY
	EASY TO PERFORM	
TRANSCRANIAL DOPPLER	CONTINUOUS	TECHNICIAN COST
	DETECTS EMBOLI	15% HYPEROSTOSIS
	?EASY TO INTERPRET	LOSS OF SIGNAL
SOMATOSENSORY EVOKED POTENTIAL	FUNCTIONAL	TECHNICIAN COST
	CONTINUOUS	
ELECTROENCEPHALOGRAPHY	CONTINUOUS	TECHNICIAN COST
NEAR – INFRARED SPECTROSCOPY	EASY TO APPLY	SCALP INTERFERENCE
	CONTINUOUS	

Table 9.2. Cerebral desaturation by sensor type and site

Site	**Neurological Deficit** **(% change, range, mean, SD)**	**No Neurological Deficit** **(% change, range, mean, SD)**
Ipsilateral Frontal	2.5 – 14 (6.44; 3.57)	0 – 7 (2.34 – 1.56)
Ipsilateral Temporal	2 – 8 (3.5; 2.14)	0 – 8 (2.07 – 1.86)
Contralateral Frontal	0 – 4.5 (2.25; 2.25)	0 – 2.5 (0.25; 0.25)
Jugular Venous Saturation	10 – 15 (12.5; 2.5)	0 – 12 (2.4; 4.18)

Figure 9.1. Changes in RSO2 at cross clamping, Temporal probe, neurological deficit vs no neurological deficit

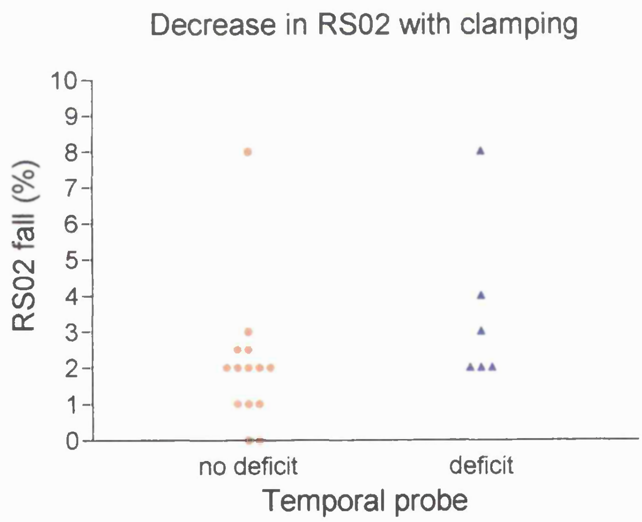


Figure 9.2. Changes in RSO2 at cross clamping, Frontal probe, neurological deficit vs no neurological deficit

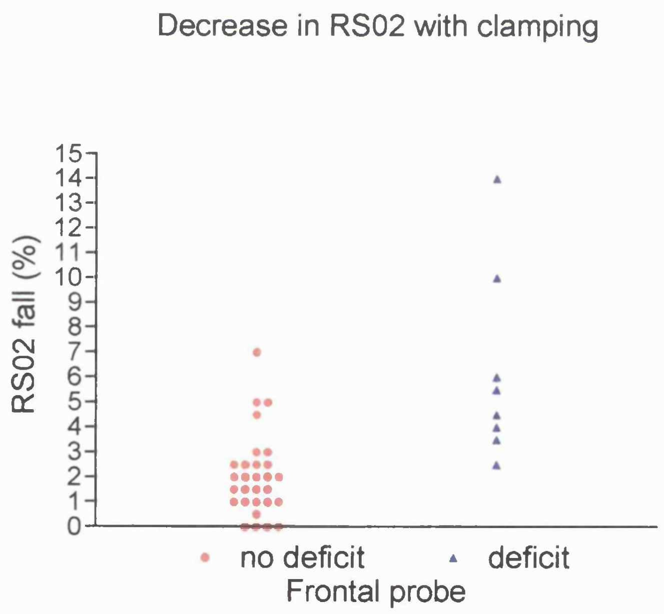


Figure 9.3. Changes in Jugular Venous Saturation, neurological deficit vs no neurological deficit

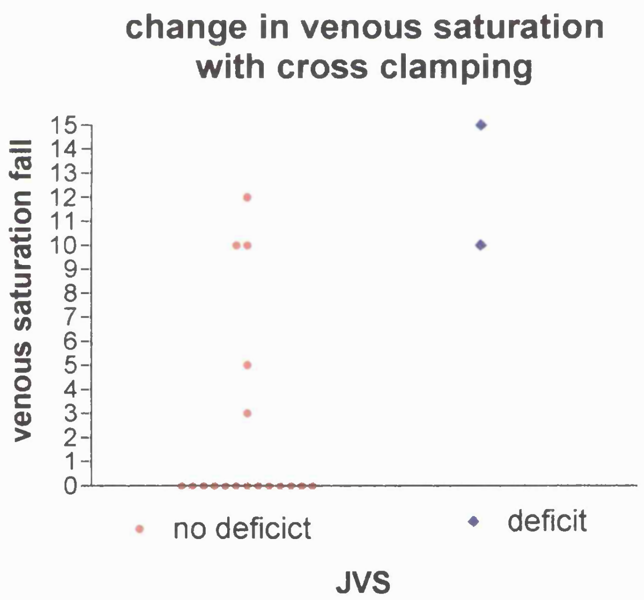
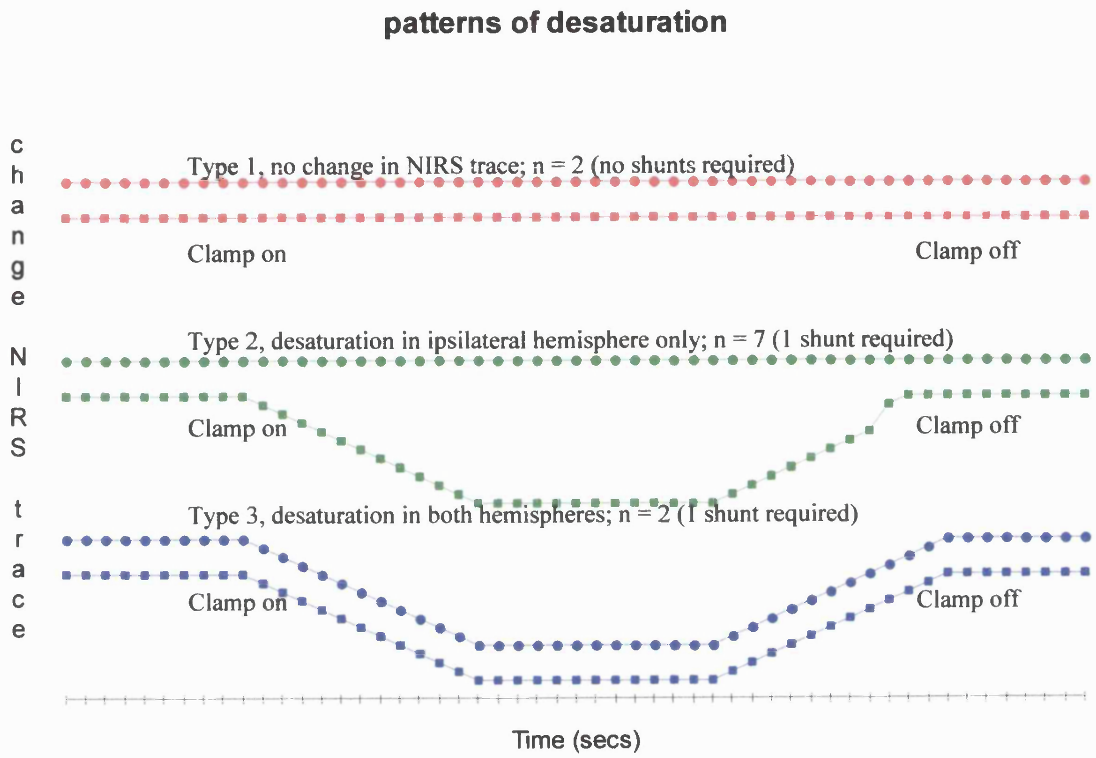


Figure 9.4. Different patterns of bifrontal desaturation with carotid cross clamping



The above diagram illustrates that different patterns of desaturation can be seen between subjects. Prediction of the need for a shunt by the pattern is difficult since both unilateral and bilateral change can be associated with shunt requirement, with neither being specific or sensitive.

Discussion

The European and North American trials of surgery versus best medical management have shown a benefit from surgery. If it is to remain an effective therapy the complication rates neurological need to be as low as possible. One of the ways the operating surgeon can reduce complications is to minimise the potential cerebral hypoxia that carotid cross clamping can cause by either performing the procedure under locoregional anaesthesia and assessing the effect clinically or by using shunts on a selective or mandatory basis. Selective shunting would appear sensible since only 15% of local anaesthetic procedures require a shunt and inserting the device involves additional dissection and the process of insertion may cause intimal damage to the vessel. For selective shunting to be targeted one requires a monitor with a safe threshold at which to intervene which is both sensitive and specific. Ideally the system should be affordable, easy to use and portable enough to be brought into operating theatre. Of the available systems none to date has all the above abilities, although with time regular users become familiar with their systems and develop their own personal criteria for shunt insertion.

Near - infrared spectroscopy is at first sight a very attractive monitoring system since it is robust, portable, easy to use and has worked on 85% of the patients in our series making it as effective as TCD, but without the need for technician and with a higher successful monitoring rate when the frontal position is used. NIRS demonstrates changes in cerebral saturation in real time and does not miss any significant desaturation. Additionally, sensor failure was not due to any fault with the equipment but rather to the inability of the adhesive tape to hold it in place in the presence of heavy sweating and problems with laptop software which did not effect the data available in theatre but stopped recording to disc. The system showed a statistically significant difference in desaturation between those requiring a shunt for neurological deterioration and those who were not effected by cross clamping, which would indicate that it does give a true reflection of cerebral ischaemia and as a consequence should be a very useful intra - operative monitor in those receiving surgery under general anaesthesia.
The difficulty with recommending its use comes from the subtle but very important difference between a statistically significant and a clinically significant change Additionally

this study has a relatively small number of patients in it and so there is the danger that statistical significance has been achieved by an inadequate sample size rather than a true difference between patients; caution in interpreting figures is therefore urged.. If one were to use the lower limit of desaturation associated with neurological deterioration in the ipsilateral frontal probe one would insert an additional, clinically unnecessary 18 shunts to give an overall shunt rate of 26/52 (50%). Although this does avoid the insertion of a large number it is obviously not as accurate as one would desire and if shunts were to be used this frequently one could suggest that a policy of mandatory shunting would be a safer option. Additional or alternative monitoring at the temporal site will not improve the situation since there were less profound changes at this site.

Simultaneous monitoring of the contralateral side was performed since it was presumed that this would demonstrate "steal" from the non - operated hemisphere which should only occur in situations of low perfusion with attendant cerebral compromise. This desaturation should only occur in situations of significant cerebral ischaemia and so should be associated with neurological deterioration, but in 1 of the 2 cases with this pattern there was no fall in level of consciousness and so it does not improve specificity. Although in making this statement one acknowledges that it could be a function of the small number of patients which have been studied and possibly continued bilateral awake monitoring should be performed to try to discover if the type 3 desaturation pattern is a marker for cerebral dysfunction. Even if subsequent work did show that type 3 should be shunted it will not assist the surgeon with the majority of patients who have a type 2 desaturation which can be associated with dysfunction. The "safe" option for these would again be to insert a shunt, and only not shunt those with a type 1 desaturation.

The same problem of clinical versus statistical significance also applies to the 20 cases where JVS monitoring was used; although the mean saturation is significantly different between those with decreased level of consciousness compared to those without, the overlap is marked and would have raised the intervention rate from 10% to 25%. JVS monitoring is also expensive (each probe costs £100 and is single use) and the changes take time to develop.

The poor results of this study in the presence of a seemingly accurate system are obviously disappointing and need explanation. The first explanation is that the different skull geometries of the individuals are having a major effect on the pathlength of the NIR light making any comparisons between subjects impossible. We do not think this is the case since our cadaveric work has shown that the system does demonstrate unit changes between subjects in the same manner, but with the lack of quantification we do not know whether the patients are actually starting from the same baseline. It may be that some of them are at the limit of their cerebral reserve at the commencement of the case and so only require a marginal change to render them neurologically impaired.

The second explanation is that each person studied has differing degrees of intra and extra - cranial atherosclerosis with variable reserve. It would seem likely that some individuals will have "watershed" areas of brain tissue which have tenuous supply reliant on optimal blood flow, with any interruption causing deterioration. A previous awake NIR study[(178)] in a small number of patients having carotid endarterectomy found that two of sixteen patients were very sensitive to hypotension and developed signs of global ischaemia which resolved on restoration of blood pressure. Due to the limited area of tissue analysed by NIRS it is not possible to assess all regions and so "critically ischaemic" patches of the brain may not cause a change in the NIRS trace although clinically they will have a profound effect. The challenge will be to attempt to identify a method of accurately assessing this peri - operatively, which NIRS in its current application does not do.

Conclusion

In this group of patients shunt insertion was required in 15% of cases. Near - infrared spectroscopy may be able to show the changes in cerebral oxygen saturation with time but it is not useful as an indicator of the need to shunt since it would over - predict in approximately 35% of patients if ipsilateral frontal monitoring were used. Accuracy is not improved by the addition of a second NIRS sensor in either the ipsilateral or contralateral hemisphere. The addition of a further monitor of global cerebral oxygenation (jugular venous saturation) does not assist in deciding who to shunt.

Chapter 10 Summary and Discussion

Introduction

The purpose of the research projects contained in this thesis were to assess the ability of near - infrared spectroscopy to measure change in cerebral oxygenation and to establish whether these observed changes have any relevance to clinical practice.

Cadaveric studies

The cadaveric studies revealed that the system can penetrate the human cranium and reproducibly detect changes in the quantity of oxygenated haemoglobin contained therein. These studies also showed that there was marked inter - subject variation which means that it will not be possible to provide a "normal" range of cerebral oxygenation. The current near - infrared system will be useful as an assessor of change in an individual with time, but does not have the capability of providing the clinician with an indicator of whether the individual's cerebral oxygenation was normal when first measured. This restricted ability means that NIRS cannot be used in as many applications as first hoped by the manufacturer, especially in the assessment of acute resuscitation in those with both traumatic injuries and medical emergencies where the initial baseline of the patient may be grossly abnormal.

Clinical studies

With this limitation in mind the system was used to good effect in the situation of carotid surgery where the patient is monitored pre - carotid clamping and so allows a baseline of the patient's own normal cerebral oxygenation, which may or may not change with application of carotid clamps. These changes have been observed and due to their temporal association with internal carotid clamping it would appear that they are related to cerebral rather than cutaneous changes. Clamping the external carotid artery does have an effect on the NIRS trace, albeit small, which will be due to a combination of alteration in cutaneous flow and to the small contribution that the external carotid circulation makes via collaterals to the intra - cerebral blood supply.

If NIRS were being used as an intra - operative monitor the recommendation would be to selectively clamp the internal carotid and wait for the trace to establish a new steady state prior to further clamp application. This will allow the operating surgeon to assess the effect of the single variable of change in cerebral blood flow without the confounding influence of change in cutaneous signal.

Probes can be positioned at either the frontal or the temporal positions, but the frontal would be the site that one would recommend due to its ease of application, reliability of recording, acceptability to the patient and ease of maintenance throughout the operation.

The lack of ability in providing a sensitive and specific level of desaturation which is associated with neurological deficit is disappointing. The first explanation for this is that the probe was not situated over an area of brain which was "critically ischaemic" and that if we had been able to pre - operatively identify areas of reversible ischaemia and locate probes accordingly then we would have had better results. Theoretically this could have been achieved by using SPECT scans to map the brain and identify areas of hypoperfusion, but this modality was not available. Without this "brain map" our options were limited to the application of two probes and the measurement of jugular venous saturation hoping that this would demonstrate regional or global cerebral ischaemia and that there would be a consistent change associated with neurological dysfunction.

The second explanation is that each patient has a different hypoxic reserve which means that there is no absolute threshold of desaturation which will reproducibly be associated with neurological deficit across a range of people. This may well be true in view of the wide range of TCD flow readings which can or cannot be tolerated by those receiving carotid surgery under local anaesthetic. This could be proved by taking a sample group of normal subjects and giving them increasingly hypoxic gas mixtures to breathe to allow their PO2 to fall in increments of 0.5KPa and see if there is a fixed level at which neurological events occur, but this is unlikely to be ethical in view of the risk of hypoxic brain injury to an otherwise healthy group.

The third explanation is that the brain tissue has in some patients already been damaged and has areas of infarction, leading to impaired diffusion of oxygen into tissues. This would not be clinically apparent under normal conditions, but would become obvious at times of hypoxia. To assess this would require pre - operative MRI scans to look for areas of micro

– infarction, with an attempt at predicting symptoms on cross clamping by relating the anatomical position of the infarct with the function at that site. Obviously this would be an expensive undertaking.

The last explanation is that the equipment was faulty and that it failed to record the desaturation accurately, but the cadaveric studies would appear to refute this.

Emboli

Also disappointing is the inability to detect changes in cerebral oxygenation with cerebral emboli. This may be due to the small number of embolic events observed and the it is possible that with further study desaturation would be observed. The NIRS showed regional saturation to one decimal point and so the limit of demonstration of change would be 0.1%. The smallest change in RSO2 seen at carotid cross clamping was 0.5%, leading to the conclusion that the embolic load needed to cause a detectable change would have 20% of the impact of a carotid cross clamp, indicating a large cerebral insult. Sensitivity could be improved by demonstrating RSO2 to two or three decimal places thereby illustrating smaller degrees of change, but RSO2 is derived from comparison of oxygenated and deoxygenated haemoglobin in the tissues which are already being measured in micromolar quantities, to derive a three decimal place RSO2 from this would be almost certainly introduce a large margin of error and be of doubtful accuracy.

Discussion

Any of the above limitations are not restricted to solely to NIRS. As previously mentioned in this thesis all the currently employed monitoring systems have false positive and false negative rates which makes them unreliable as intra - operative monitors. This leaves the operating surgeon with a dilemma; the purpose of monitoring is to avoid the potential complication associated with the use of shunts, but if it is unreliable one will have to insert a shunt regardless. The only true gold standard for assessing cerebral function is the patient themselves and this can only be achieved under local anaesthesia.

Where monitoring may have a place is to record change during dissection as a quality control modality, with TCD and its ability to detect emboli as the single most useful tool.

This enables the operating surgeon to modify their technique, or if supervising a trainee advise them to alter their approach. Additionally TCD has the advantage of being able to detect post endarterctomy embolic load which allows the surgeon to either anticoagulate and continue to monitor, or re - operate depending on the cerebral embolic load.

Conclusion

In conclusion, NIRS can measure changes in intra - cerebral oxygenation but this information is not of help in deciding who to shunt under general anaesthesia. At present there is no other monitor commercially available which is sensitive and specific enough to do this. The common sense approach would be to perform carotid surgery under local anaesthesia whenever possible and employ a strategy of selective shunt insertion dependant on the patients condition. If the surgery has to be performed under general anaesthesia then mandatory shunt insertion would appear the safest option to avoid potential hypoxic sequelae in the 15% of patients who do require shunts.

If one wishes to use a monitor the most suitable is TCD, but in its role as a quality control and emboli detection modality rather than as a flow meter to decide upon shunt insertion.

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Appendix 1

Patient Details

Table App.1. Age and Gender

Operation (no cases)	Female	Male
Carotid aneurysm (1)	1	0
Age	45	0
Carotid endarterectomy (76)	22	54
Mean age (range)	72.3 (62 – 80)	67.7 (51 – 84)

Table App.2. Indication for operation

Indication for operation	Number of cases
Aneurysm	1
Transient ischaemic attack	33
Stroke	11
Amaurosis Fugax	15
Pre – CABG	7
Asymptomatic	9
Dizziness	1

Table App.3. Patient Risk Factors

Risk Factor	Number of patients
Hypertension	33
Diabetes	10
Peripheral vascular disease	9
Cardiac disease (MI or angina)	30
Hyperlipidaemia	12
Single risk factor	61
Two risk factors	42
Three risk factors	11

Table App.4. Pre operative Investigations

Investigation	Number
Duplex	77
Angiogram	4
MRA	4
CT Brain	8

Appendix 2

Refinement of locoregional technique

Local anaesthetic

The long acting local anaesthetic Bupivicaine is well suited to the deep and superficial blockade but has several drawbacks for use intra – operatively. Firstly it has a slow onset of action and secondly causes fits if inadvertently injected into the arterial supply to the brain. We moved to the intra – operative use of Prilocaine which is much quicker in its onset of action and safer to use.

Anxiolysis

For any local anaesthetic technique to be acceptable to both patient and surgeon one requires a balanced triad of anaesthesia, anxiolysis and analgesia. Anaesthesia is provided by a mixture of short and long acting local anaesthetics, analgesia by use of opioates and non – steroidal anti – inflammatory agents and anxiolysis by a relaxed enviroment in the operating theatre, distracting conversation and pharmacological agents.

One of the most important tasks in theatre is to distract the patient and to talk about any subject other than the operation. This seems like a simple task but not all people can hold a conversation with a patient for up to two hours and keep them entertained, ladies anecdotally seemed to be much better at it than men.

We found that giving the patients a premedication with Temazepam and Phernegan meant that they were relaxed throughout the procedure but without significant cognitive impairment. In the first cases we did not do this but instead gave bolus doses of intravenous Midazolam, but found that this dissociated the patients from their surroundings and often amplified the (understandable) fear that they had and made the surgery very difficult. Since the use of a premed this has not been the case.

Comfort

Under general anaesthesia patients lose the ability to thermoregulate, move and control urination, which is why warming devices, padding and urinary catheters are used. Under locoregional anaesthesia all of these are still present and under control and so we modified our systems accordingly. Firstly the patient was not catheterized and the anaesthetists told not to be over zealous with intravenous fluid administration since this caused problems with requirement for a mid – operation urination in our first case. Secondly the patient must be given time to adjust their position to a comfortable one since they will be relatively static for two or more hours. Thirdly the warming blanket must not be employed or else the patient will become too hot and irritable.

Cognitive assessment

At carotid cross clamping the patient may have neurological impairment, but the only way to assess this is to establish a pre – clamp baseline of function. The easiest way to do this is to ask the patient a series of questions related to their personal life (address, children's names, significant dates in their life), mental tasks (arithmetic, reverse alphabet) and motor tasks (wriggling toes, squeezing a squeaky toy) and then ask the same questions again post clamping. Occasionally the patient will have an immediate change in level of consciousness, but often it a slower deterioration over a period of minutes. In this latter, more commonly encountered situation, one usually notes that the patient loses their sense of humour first, then their ability to hold a rapid conversation and only latterly do they have a more marked neurological compromise. Once this pattern of deterioration is noted a shunt is used, being associated with an improvement in function. If the deterioration is very slow and the endarterectomy very straight forward without the need for a patch it is possible to finish the endarterectomy without a shunt, but this is an unusual occurrence.

Appendix 3

Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACE	Acetylsalicylic acid and Carotid Endarterectomy Trial
ACST	Asymptomatic Carotid Surgery Trial
ADP	Adenosine Diphosphate
AF	Atrial Fibrillation
ATP	Adenosine Triphosphate
BP	Blood Pressure
BPG	Biphosphate Glycerol
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CBF	Cerebral Blood Flow
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
CO_2	Carbon Dioxide
CT	Computerised Tomography
CVA	Cerebrovascular accident
Cyt aa_3	Cytochrome aa_3
DL	Distal Lumen
DSA	Digital Subtraction Angiography
ECA	External Carotid Artery
ECG	Electrocardiogram
ECST	Eurpoean Carotid Surgery Trial
EEG	Electroencephalogram
FAD	Flavine Adenine Dinucleotide (oxidised)
$FADH_2$	Flavine Adenine Dinucleotide (reduced)
GA	General Anaesthesia
GALA	General Anaesthesia versus Local Anaesthesia in Carotid Endarterectomy
H^+	Hydrogen ion

HbO_2	Oxygenated Haemoglobin
HHb	Deoxygenated Haemoglobin
Hz	Hertz
ICA	Internal Carotid Artery
JVS	Jugular Venous Saturation
LA	Local Anaesthesia
LDL	Low Density Lipoprotein
LED	Light Emitting Diode
MCA	Middle Cerebral Artery
mg	millegrams
ml	millelitres
MRA	Magnetic Resonance Angiography
MRDSA	Magnetic Resonance Digital Subtraction Angiography
MRI	Magnetic Resonance Imaging
MRL	Minimal Residual Lumen
MV	Mean Velocity
NAD	Nicotine Adenine Dinucleotide (oxidised)
NADH	Nicotine Adenine Dinucleotide (reduced)
NASCET	North American Symptomatic Carotid Endarterectomy Study
NIR	Near Infrared
NIRS	Near Infrared Spectroscopy
nm	Nanometres
O_2	Oxygen
O_2Hb	Oxygenated Haemoglobin
OPG	Oculoplethsmography
PC	Personal Computer
PI	Pulsatility Index
PO_2	Partial Pressure Oxygen
PSV	Peak Systolic Velocity
RIND	Reversible Ischaemic Neurological Deficit
rSO_2	Regional Saturation

SPECT	Single Positron Emission Tomography
SSEP	Somatosensory Evoked Potentials
TCD	Transcranial Doppler
tHb	Total Haemoglobin
TIA	Transient Ischaemic Attack
W	Watts